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Review

Advances in *S. cerevisiae* Engineering for Xylose Fermentation and Biofuel Production: Balancing Growth, Metabolism, and Defense

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Abstract: Genetically engineering microorganisms to produce chemicals has changed the industrialized world. The budding yeast *Saccharomyces cerevisiae* is frequently used in industry due to its genetic tractability and unique metabolic capabilities. *S. cerevisiae* has been engineered to produce novel compounds from diverse sugars found in lignocellulosic biomass, including pentose sugars, like xylose, not recognized by the organism. Engineering high flux toward novel compounds has proved to be more challenging than anticipated since simply introducing pathway components is often not enough. Several studies show that the rewiring of upstream signaling is required to direct products toward pathways of interest, but doing so can diminish stress tolerance, which is important in industrial conditions. As an example of these challenges, we reviewed *S. cerevisiae* engineering efforts, enabling anaerobic xylose fermentation as a model system and showcasing the regulatory interplay's controlling growth, metabolism, and stress defense. Enabling xylose fermentation in *S. cerevisiae* requires the introduction of several key metabolic enzymes but also regulatory rewiring of three signaling pathways at the intersection of the growth and stress defense responses: the RAS/PKA, Snf1, and high osmolarity glycerol (HOG) pathways. The current studies reviewed here suggest the modulation of global signaling pathways should be adopted into biorefinery microbial engineering pipelines to increase efficient product yields.

Keywords: xylose fermentation; signal transduction; yeast; environmental stress response; protein kinase A

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1. Microbes Serve as Outstanding Chassis for Biochemical Production

Since the early days of genetic manipulation, microbial engineering through genetic change has revolutionized how chemicals and products of interest to human society are produced. The feasibility of genetic modification, coupled with tractability, ease of culturing, and fast replication rates of the budding yeast *Saccharomyces cerevisiae* and certain bacteria, like *Escherichia coli*, *Lactobacillus*, and others, allow for microbial engineering to produce large yields of designated products in a short period of time. It is now feasible to introduce whole exogenous pathways into *S. cerevisiae* or *E. coli* to produce novel compounds, such as natural plant products like the drugs noscapine and resveratrol [1]. Expressing whole biosynthetic pathways in yeast or bacteria dramatically increases the yield while decreasing necessary resources, allowing for more cost-effective production of bio-products used as flavors, fragrances, and medicines [1]. Another rationale for microbial engineering is to utilize and manipulate an organism's fundamental physiology. A unique characteristic of *S. cerevisiae*'s biology is its preference for fermentation for energy production, even under aerobic conditions, a characteristic that has been exploited by humans to brew beer, ferment wine, and produce bread for thousands of years [2–5]. While fermentation is far less energy efficient than cellular respiration, it gives the yeast a competitive advantage

in nature: fermentative flux is much faster than respiration, allowing yeast to proliferate faster than other microorganisms. The production of ethanol during fermentation also inhibits the growth of other microorganisms, reinforcing the selective pressures on the yeast to preferentially ferment preferred carbon sources [6]. Once scientists identified yeast as the organism responsible for beer and bread, it was only a matter of time before research techniques advanced enough to manipulate the physiological traits of yeast for industrial purposes.

Modulating innate metabolic pathways like fermentation in *S. cerevisiae* is advantageous because the cell has evolved for millennia to perform that fundamental function. However, this can also become a disadvantage since free-living microbes have evolved to maximize growth when nutrients are plentiful or limit unneeded metabolism and growth to mount a robust stress response under suboptimal conditions (Figure 1). In the remainder of this review, we use "stress response" to refer to any response to an environmental stimulus, whereas "defense" is the aspect of that response that is intended to protect against the stimulus and maintain fitness. An important component of microbial engineering strategies is to drive the pathway flux toward product formation and away from biomass production (i.e., growth) and costly stress defense systems to optimize the product yield (Figure 1) [7–10]. This requires an understanding of not only the metabolic pathway being engineered but also how that pathway is regulated and integrated with a cellular system.

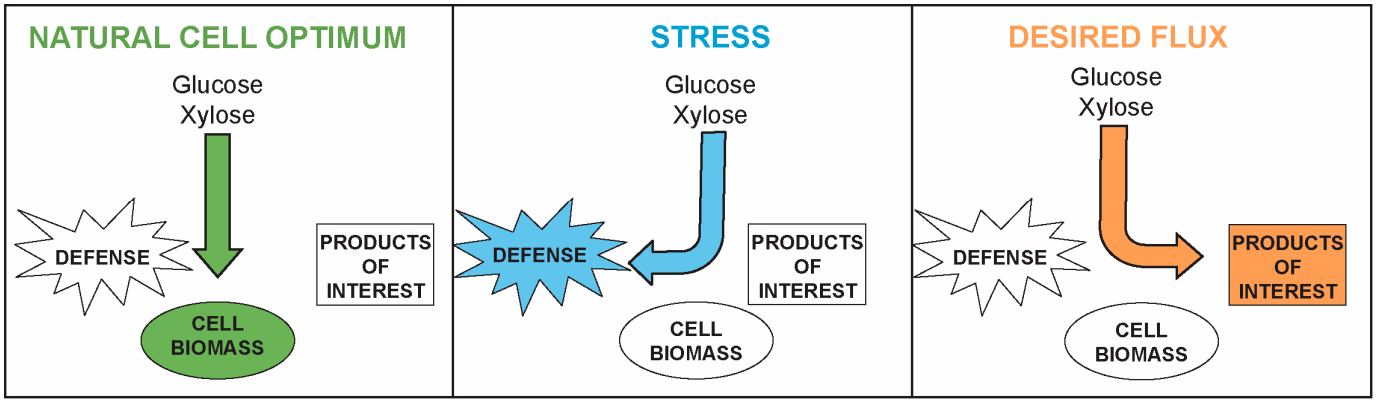

Figure 1. Overview of different cellular regimes that prioritize growth, stress defense response, or engineered metabolic flux in biofuel-producing microorganisms. See text for details.

At the same time, stress tolerance is important for industrial conditions. For example, plant material used to make sustainable fuels must be chemically and/or physically broken down to release the sugars from the biomass, forming a slurry called hydrolysate. The chemicals used to break down lignocellulosic biomass, as well as toxins released from the plants themselves, can inhibit the microorganisms in later steps [11–23]. Additionally, the composition and concentration of toxins released from the plants change between crop years, depending on the plant's environmental growth conditions [11,24–29]. Ultimately, successful engineering strategies will require the production of stress-tolerant strains in a way that does not compete with cellular resources that are being directed to product formation. A deeper understanding of how cells have evolved to balance growth, metabolism, and stress defense—and how to modulate that through engineering—is required.

2. Rapid Growth and Maximal Stress Tolerance Are Competing Interests in Cells

Our understanding of how growth, metabolism, and defense are integrated into cellular regulatory networks is only beginning to emerge, but recent studies have uncovered new insights into the balance between the growth and defense controls. Rapid growth and maximal stress tolerance are competing interests in the cell since both require significant resources to enact. When times are good and nutrients are plentiful, *S. cerevisiae* maximizes its growth rate, but to do so, cells decrease the defense systems to direct resources to biomass production and division. Thus, the fastest-growing cells are typically the most

sensitive to acute stress [30–36]. In response to sudden stress, cells typically decrease their growth rate and transiently arrest their cell cycle while they redirect cellular resources to mounting the stress response, which includes mechanisms to defend against the imposing stress as well as what are likely protective mechanisms against future stresses.

A major component of the *S. cerevisiae* stress response is reorganizing the transcriptome. In addition to specialized responses triggered by specific stresses, stressed yeast mounts a common response to stress. The environmental stress response (ESR) comprises ~900 genes whose expression is altered in response to a variety of stresses, leading to massive physiological changes [37–40]. The ESR includes ~300 genes whose transcript abundance increases during stress and ~600 genes whose transcript abundance decreases. Induced genes are broadly involved in stress defense processes, including oxidation-reduction balancing, protein folding, the production of defense molecules like trehalose and glycerol, and specific regulators. The transcriptional induction of these genes is controlled by a variety of stress-specific factors in conjunction with the general stress transcription factors Msn2 and Msn4 [37,38,41–43]. In contrast, genes repressed in the ESR include genes that normally promote growth, including ribosomal protein (RP) and ribosomal biogenesis (RiBi) genes involved in ribosome production, RNA metabolism, protein synthesis, and cell growth [37].

Activation of the ESR can co-occur with the decreased growth rate of a culture, leading several studies to suggest that the ESR is intimately regulated with, and predictive of, the cellular growth rate [30,44–46]. However, work from our lab shows that the ESR is separable from growth and division: the ESR is still activated upon heat or salt stress, even in cells that are already arrested in their cell cycle with low biomass production [34]. Instead, we argue that the dramatic transcriptome changes associated with the ESR serve to accelerate a stress response. The transient repression of ribosome-related and growth-promoting genes during stress helps to redirect the transcriptional and translational capacity toward stress-induced transcripts [34,47,48]. Somewhat counterintuitively, cells that lack repressors of the repressed ESR genes, Dot6 and Tod6, grow well in the absence of stress but acclimate much slower to salt stress [48]. At least part of this mutant effect can be explained by the delayed production of defense proteins: ribosome- and growth-related transcripts stay associated with translating ribosomes in the mutant cells at the expense of stress-induced transcripts, leading to a delay in the production of stress defense proteins [34,48].

The ESR is regulated by multiple upstream signaling pathways, many of which are only activated by specific conditions [33,34,37,38]. Among the best studied of these are the protein kinase A (PKA), Snf1, and high osmolarity glycerol (HOG) pathways, all of which turn out to be important for engineered xylose fermentation (reviewed in more detail below). PKA inhibits the ESR in part by phosphorylating and inhibiting Msn2/4, Dot6/Tod6, and other regulators [49,50]; it also functions to modulate gene expression of specific genes by binding promoters and coding regions via interactions with chromatin proteins or the RNA polymerase [51–54]. Snf1 and HOG can also modulate downstream ESR regulators, including Msn2/4 and others, both directly and indirectly [41,55–57]. Interestingly, several independent studies found that modulating the activity of these broadly acting signaling pathways is necessary to promote robust anaerobic fermentation of xylose in engineered biofuel yeast strains (see below). The remainder of this review will discuss the potential roles of the PKA, Snf1, and HOG pathways in engineering xylose fermentation.

3. Engineering Yeast for Ethanol Production from Lignocellulosic Biomass

With its innate proclivity to ferment, *S. cerevisiae* was adopted early for the production of ethanol as a biofuel [58]. While biofuels serve as a renewable fuel source compared to fossil fuels, significant work remains to make their production efficient and sustainable. For example, a major shift in biofuel research was the switch in focus from crop plants, like corn, to lignocellulosic feedstocks as biomass sources for biofuel production [59–62]. Lignocellulosic feedstocks do not compete with food supply, and they are widely abundant and grow on land less suitable for food crop farming [59–62]. Another shift in bioenergy research has been to produce higher-energy biofuels, like isobutanol, which is less hygro-

scopic and has a higher energy density than ethanol, making it more efficient to use in engines [59,62–69]. Engineering robust isobutanol production in yeast is an active area of research that comes with some challenges, explored recently in these extensive studies and reviews: [64,65,67–77].

Maximizing product yields per cell and biomass input requires the conversion of all carbon in the lignocellulosic biomass. This presents a significant bottleneck for efficient biofuel production: several sugars, like the pentose sugar xylose, are prevalent in lignocellulosic biomass, in addition to glucose [78,79]. However, many biofuel organisms, including *S. cerevisiae*, do not natively recognize xylose as a fermentable metabolite, thus limiting product yields when cells leave a large fraction of the sugars unconverted [79]. Thus, a major focus in microbial biofuel research has been the rational engineering of yeast strains to promote robust xylose fermentation.

One strategy has been to learn from other fungi that consume xylose (but often lack other useful traits found in *S. cerevisiae*), and several studies identified genes that, when overexpressed in *S. cerevisiae*, enable or improve xylose metabolism (e.g., *GYC1*, *YPR1*) [80–82]. Other studies have used rational engineering and directed laboratory evolution to obtain xylose-fermenting *S. cerevisiae* strains [79,83,84].

Rational design to date starts with the cloning of either xylose isomerase (XI) or xylose reductase, paired with xylitol dehydrogenase (XR/XDH) to convert xylose into D-xylulose for metabolism in the pentose phosphate pathway and central carbon metabolism [79,85–87]. However, these enzymes are not enough to support xylose fermentation, with several groups showing that other genetic modifications are required to generate a robust xylose-fermenting strain [79,88–95]. For example, collaborative research in our center, the Great Lakes Bioenergy Research Center, discovered that robust anaerobic xylose fermentation also requires null mutations in the iron–sulfur cluster's biogenesis chaperone *ISU1*, the stress response MAP kinase *HOG1*, the RAS/PKA inhibitor *IRA2*, and the aldose reductase *GRE3* [96]. Other groups using different strain backgrounds have identified similar suites of mutations [89,90,94]; for example, dos Santos et al. (2016) identified nullifying mutations in *ISU1* and a different member of the Hog1 pathway, *SSK2* [97].

Further work showed that these mutations serve to rewire upstream cellular signaling, pushing the metabolic flow toward metabolism and away from stress responses. Multi-omics studies in our lab discovered major signaling rewiring, causing the simultaneous activation of the growth-promoting signaling pathway, PKA, with the Snf1 pathway, which normally responds to poor carbon sources [98]. PKA is generally active when cells are grown in optimal conditions with glucose as the carbon source, whereas Snf1 is active under suboptimal conditions with non-glucose carbon sources [99,100]. While these pathways share many of the same targets, they have opposing functions and, thus, are not typically active at the same time [99,100]. The physiological impacts of these signaling alterations remain incompletely understood. Furthermore, multiple studies have implicated null mutations in Hog1, which is important both for glucose responses and stress tolerance [101–103]. Below, we discuss these pathways and their interplay with growth, metabolism, and defense.

4. Key Regulators That Govern Physiological Pathways Rewired for Xylose Fermentation

The PKA, Snf1, and HOG signaling pathways are conserved throughout eukaryotes. All three pathways mediate global changes to the cell in response to a changing environment. While each of these pathways has been extensively studied on their own, how their activity is coordinated with each other and with the cell cycle and metabolism remains poorly understood, thus making it difficult to fully understand their roles in xylose utilization.

4.1. Protein Kinase A Pathway

The PKA pathway is one of the best-characterized signaling pathways in eukaryotes. PKA is a growth-promoting kinase, and its main function in microbes is to induce cellular activities that support rapid carbon metabolism and proliferation while simultaneously inhibiting stress responses [104–106]. PKA can directly phosphorylate metabolic enzymes to alter biosynthetic flux (e.g., Cdc19, Pyk2, Nth1, and Pfk26), as well as modulate gene expression via the phosphorylation of transcription factors (e.g., Msn2/4, Dot6/Tod6, and many others) and other regulatory kinases (e.g., Yak1) [43,49,104,107–110]. It is well established that hyperactive PKA prevents growth on non-fermentable sugars via modulating glycolytic enzyme activity, but perhaps also other effects [104]. Strains in which PKA is hyperactive are also sensitive to many types of environmental stressors, such as heat and oxidative stress, consistent with its role in suppressing the stress response [111]. PKA's role in modulating carbon metabolism is tightly linked with progression through the cell cycle, ensuring that cell functions are supported by the proper nutrients (discussed below). Thus, the PKA pathway must be highly regulated to ensure it is activated appropriately for the conditions.

More recent evidence indicates that PKA may have different effects depending on how it is activated. PKA is a heterotetrameric enzyme composed of two catalytic subunits (encoded by the *TPK1/2/3* genes) and two regulatory subunits (encoded by the *BCY1* gene; Figure 2) [111–113]. PKA is thought to be inactive via association with Bcy1 but can become active when cAMP binds Bcy1, releasing the catalytic subunits [99,105]. cAMP is produced by the adenylyl cyclase Cyr1 [114–116], which, in yeast, is regulated by two different upstream branches, both activated by the presence of glucose in the environment and the cell. One branch contains the transmembrane G-protein-coupled receptor Gpr1 that binds to external glucose and relays the signal to Cyr1 via Gpa2 (Figure 2) [99]. The second branch involves Ras1/2 GTPase proteins that activate Cyr1 for cAMP production. The guanine nucleotide exchange on Ras1/2 is stimulated by the guanine exchange factors (GEFs) Cdc25 and Sdc25 (Figure 2), which are activated by glucose but do not directly sense glucose [117–119]. It is hypothesized that the phosphorylation of glucose to glucose-6-phosphate and the subsequent acidification of the cytosol activates the GEFs, but the exact mechanism remains unknown [120–123]. This process is inhibited by the GTPase-activating proteins Ira1/2 that convert Ras1/2 to the inactive GDP-bound form [124–127]. cAMP concentrations are also regulated by a feedback mechanism composed of PKA and the phosphodiesterases (PDEs) Pde1/2, which degrade cAMP into AMP (Figure 2) [128–131].

There are multiple modes of regulating the RAS/PKA pathway apart from cAMP production. A particularly interesting mode that remains poorly understood is through spatial control. Each of the yeast PKA subunits has its own localization patterns under varying conditions [132–134]. However, how this localization is regulated remains incompletely known. Higher eukaryotes have a variety of A-kinase anchoring proteins (AKAPs) that bind the regulatory subunit to control the PKA's subcellular localization [135]. AKAPs have tissue-specific expression and regulate PKA–substrate interactions [135–140]. They have also been described to form signalosomes, which produce micro-environments of PKA, PKA substrates, PDEs, and/or other upstream components of the PKA pathway [141,142]. This is predicted to bring PKA in contact with the substrates and quickly and dynamically regulate PKA activity via cAMP abundance [139,141–145]. While yeast does not possess recognizable AKAP orthologs, several functional analogs have been proposed [146–148]. For example, Tpk1 nuclear localization is dependent on the presence of Bcy1 [133], supporting the possibility that Bcy1 either acts as an AKAP or interacts with other AKAP-like proteins. Previous work in our lab found that adding a C-terminal tag to Bcy1 in a strain engineered for xylose metabolism is enough to enable rapid anaerobic xylose fermentation in the absence of growth [98]. This result suggests that Bcy1 has a more nuanced role in PKA regulation than simply binding and inhibiting its activity. Due to its broad roles in regulating carbon metabolism and cell growth, it is no surprise that PKA plays an important role in modulating xylose utilization.

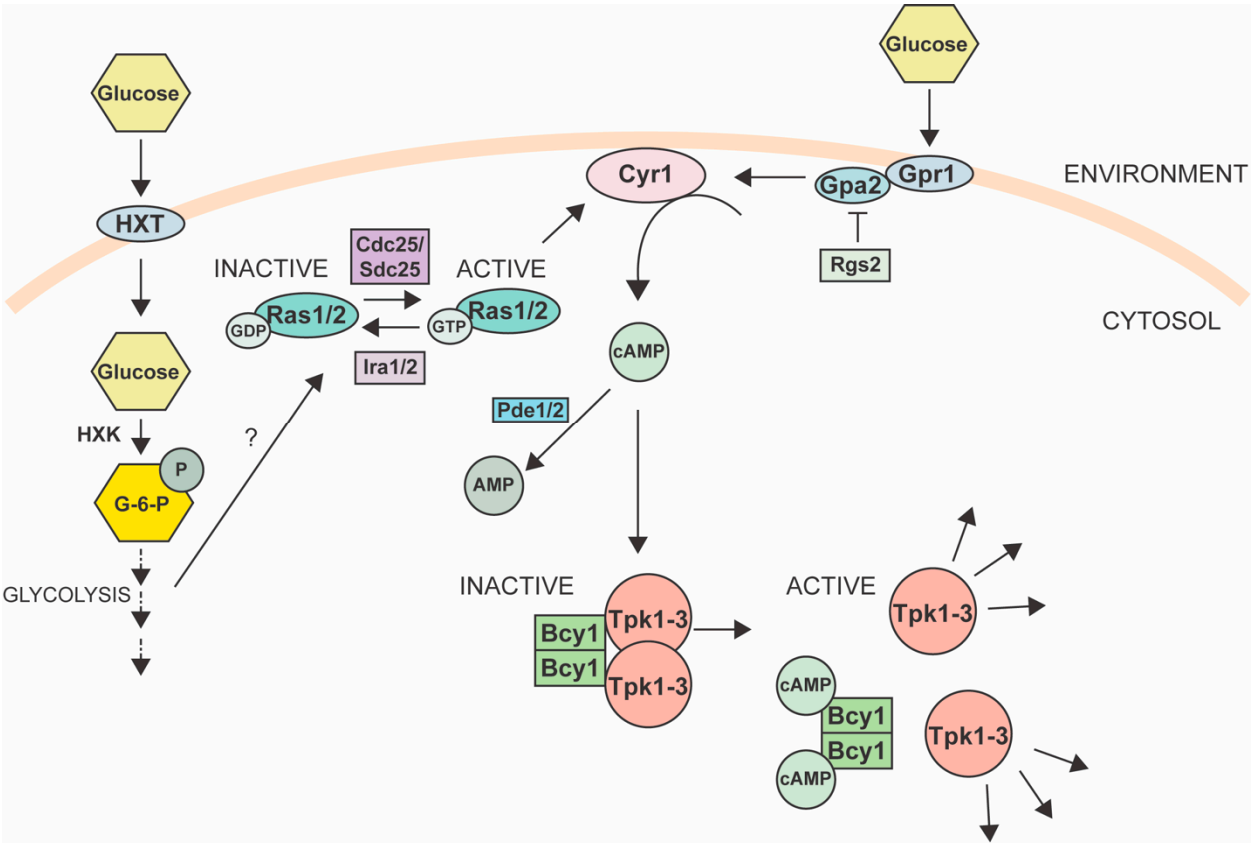

Figure 2. The Protein Kinase A pathway. A simplified view of the RAS/PKA pathway in yeast. HXTs, hexose transporters; HXK, hexokinase. See text for details [99].

Remarkably, the mode through which PKA is activated impacts xylose fermentation capabilities. Deletion of *IRA2*, in the context of xylose metabolism enzymes and *ISU1* deletion, promotes rapid anaerobic xylose fermentation and growth [96,98]. This is mediated through up-regulated PKA since blocking PKA with specific inhibitors prevents both anaerobic growth and xylose metabolism [98]. Consistent with the requirement of PKA activity, anaerobic xylose fermentation is also enabled by *BCY1* deletion; however, in this case, anaerobic growth on xylose is blocked despite robust fermentation [98,149]. Thus, the Bcy1 regulatory subunit is important for coupling PKA-dependent growth and metabolism. Recent work from our lab shows that this coupling may have to do with PKA-dependent phospholipid metabolism: anaerobic xylose growth and metabolism could be recoupled in a *bcy1*Δ strain through directed evolution. The evolved strain carries mutations in the PKA subunit, *TPK1*, and a regulator of phospholipid metabolism, *OPI1*, among other mutations, and has altered phospholipid profiles [149]. While further research will be required to fully elucidate the cellular mechanisms at play, these results show that PKA is intimately coordinated with diverse physiological processes, and engineering approaches will need to consider that coordination for successful strategies.

4.2. Snf1 Pathway

Similar to PKA, Snf1 is part of a multi-protein, nutrient-sensing complex that reorganizes the metabolism in the presence of alternative carbon sources, although it also has separable roles in the stress response [150,151]. As glucose is depleted from the environment, Snf1 becomes active to prepare the cell to switch from fermentative to respiratory metabolism, called the diauxic shift [152–156]. During this time, the cell undergoes massive transcriptional alterations. Like PKA, Snf1 interacts with a broad set of protein targets, impacting physiological processes from carbon metabolism and gene expression to intracellular trafficking and cell cycle progression [100]. Perhaps its best-characterized function is

modulating gene expression related to carbon source-dependent gene de-repression. Snf1-dependent phosphorylation of transcription factors can be activating (as for the alternative carbon source factors Adr1, Sip4, and Cat80) or inhibitory (e.g., the glucose repression factor, Mig1/2) [99,100]. Additionally, Snf1 can directly regulate chromatin accessibility and the transcriptional machinery. By phosphorylating histone H3, Snf1 recruits the SAGA complex for histone H3 lysine 4 (H3K4) acetylation [99,100]. Other work has shown a direct interaction between Snf1 and the RNA polymerase II holoenzyme, suggesting Snf1 regulates RNA Pol II activity [157,158].

The Snf1 holoenzyme contains three subunits: Snf1 is the α-subunit, which functions as the catalytic kinase; Snf4 functions as the γ-regulatory subunit; and the regulatory ß-subunit that modulates substrate interactions and complex localization is supplied as one of three proteins: Gal83, Sip1, or Sip2 (Figure 3) [159–164]. In the presence of glucose, Snf1 is inactive via autoinhibition and the Pma1-regulated intracellular pH [165]. When glucose is depleted from the environment, ADP levels rise and bind Snf4, causing a conformational change that, in turn, protects Snf1 in its active state [163,166]. During this time, Snf1 is also phosphorylated on threonine 210 (Thr210) in its activation loop with Snf4, protecting the residue from dephosphorylation. When the glucose concentration increases, the Snf1 activating protein, Std1, aggregates in puncta [167], while the Glc7-Reg1 protein phosphate complex is activated by hexokinase (Hxk2) to dephosphorylate and inactivate Snf1 [154].

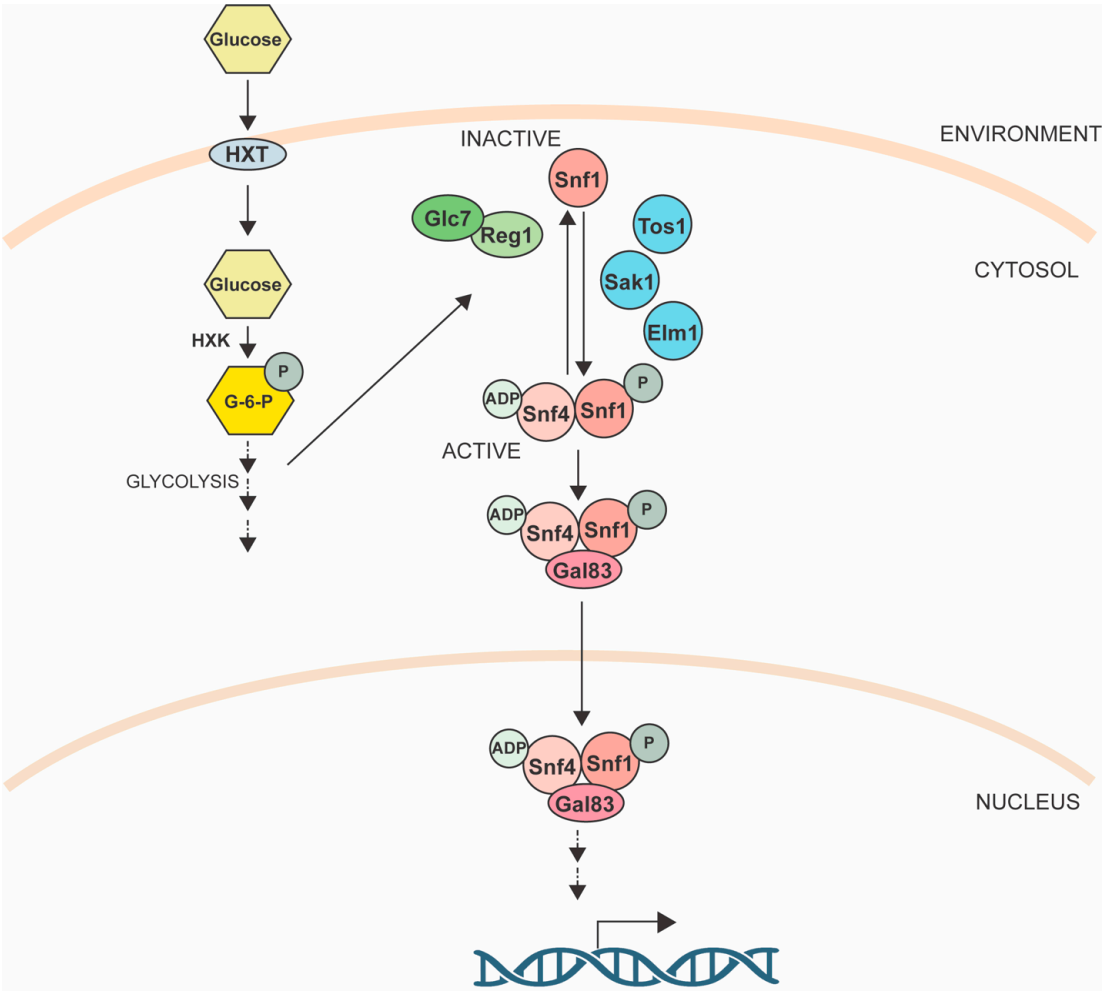

Figure 3. The Snf1 pathway. The Snf1 complex can be regulated by one of three kinases (Tos1, Sak1, or Elm1). Active Snf1 complex translocates into the nucleus to modulate gene expression. When glucose concentration increases, the Glc7-Reg1 protein phosphatase complex is activated by hexokinase (HXK) to dephosphorylate and inactivate Snf1. See text for details [154].

Even though Snf1 is best known for its role in glucose-responsive de-repression, additional functions outside of the central carbon metabolism are being established [151]. Snf1 was shown to phosphorylate and activate the ESR transcription factor Msn2 [37,55,168–170] and respond to a variety of stressors including cadmium, hygromycin B, hydroxyurea, selenite, iron, heat, oxidative stress, sodium toxicity, and ER stress [56,170–180]. Snf1 also plays a role in cell cycle regulation (see more below) and cellular aging, where in yeast, it is required to establish chronological aging in cells that have exhausted their replicative age [152,181–183].

As the PKA and Snf1 pathways both respond to a carbon source, it is perhaps not surprising that they can regulate each other. PKA controls the localization of the Snf1-Sip1 complex [184] and regulates one of the kinases that phosphorylates and activates Snf1 [185]. In return, Snf1 regulates PKA activity by phosphorylating and inhibiting the adenylyl cyclase [186]. Clearly, significant crosstalk between the Snf1 and PKA pathways exists [151]. The question of how these two opposing pathways are simultaneously activated for xylose fermentation remains unknown.

4.3. High Osmolarity Glycerol Pathway

While the PKA and Snf1 pathways respond to nutrients, the high osmolarity glycerol (HOG) pathway is best known for sensing and responding to environmental stressors, particularly changes in osmolarity. The primary effector of the HOG pathway is the mitogen-activated protein kinase (MAPK) Hog1 [103]. After osmotic stress, Hog1 becomes active by one of two upstream branches, which themselves have multiple components [103]. The Sln1 branch is composed of a MAPK signaling cascade, where the transmembrane osmosensor, Sln1, leads to downstream activation of MAP3K Ssk2/22 [187–189]. Ssk2/22 phosphorylate and activate the MAP2K Pbs2, which then phosphorylates and activates Hog1 [187,190–192]. The Sho1 branch is more complex and regulates two separate physiological responses: osmotic stress adaptation and filamentous growth. Like Sln1, Sho1 is a transmembrane osmosensor that interacts with two other transmembrane osmosensors, Msb2 and Hkr1, through a mechanism that is not fully understood. Through subsequent activation steps (Figure 4), the Sho1 branch converges with the Sln1 branch on phosphorylating and activating Pbs2, which proceeds to activate Hog1 [193]. Once active, a significant portion of Hog1 translocates to the nucleus to alter gene expression and promote the accumulation of intracellular glycerol that balances the osmolarity between the cell and environment [103,194].

The pathway can be inhibited by negative feedback. When the osmotic balance is reached between the cell and the environment, the osmosensors stop relaying a response, leading to the dephosphorylation and inactivation of Pbs2 and Hog1 [190,195–197]. Additionally, active Hog1 autoregulates its own pathway by phosphorylating players in the Sho1 branch, disrupting signaling through that branch and thus reducing Hog1 activity [198–200].

Similar to the PKA and Snf1 pathways, Hog1 phosphorylates transcription factors to modulate gene expression [201–203]. Other methods of transcriptional and post-transcriptional regulation include recruiting transcriptional machinery to chromatin, altering nucleosome positioning, and modifying mRNA stability and transport from the nucleus [103,204–207]. Hog1 can also directly regulate glycerol biosynthetic enzymes and transporters, which supports the short-term acclimation to osmotic stress [188,196,198,208–212].

Although typically thought of as an osmotic stress regulator, Hog1 can also be activated in response to a variety of environmental changes, several of which connect the Hog1 and Snf1 pathways. Hog1 is activated under both glucose stimulation and starvation in an Snf1-dependent manner that also impacts lipid signaling at the Golgi [101,102]. In contrast, Hog1 activation during ER stress is inhibited by Snf1 activity [171,213]. These studies highlight the complex nature of Hog1 activation and its requirement for competing metabolic processes. In fact, past work in our lab found that improving the stress tolerance in an engineered biofuel yeast strain by maintaining a wildtype *HOG1* reduced the specific xylose consumption rate compared to a *hog1*Δ mutant [214]. Thus, engineering an optimal

strain for biofuel production and tolerance of industrial conditions will likely require intimate tinkering of multiple signaling pathways.

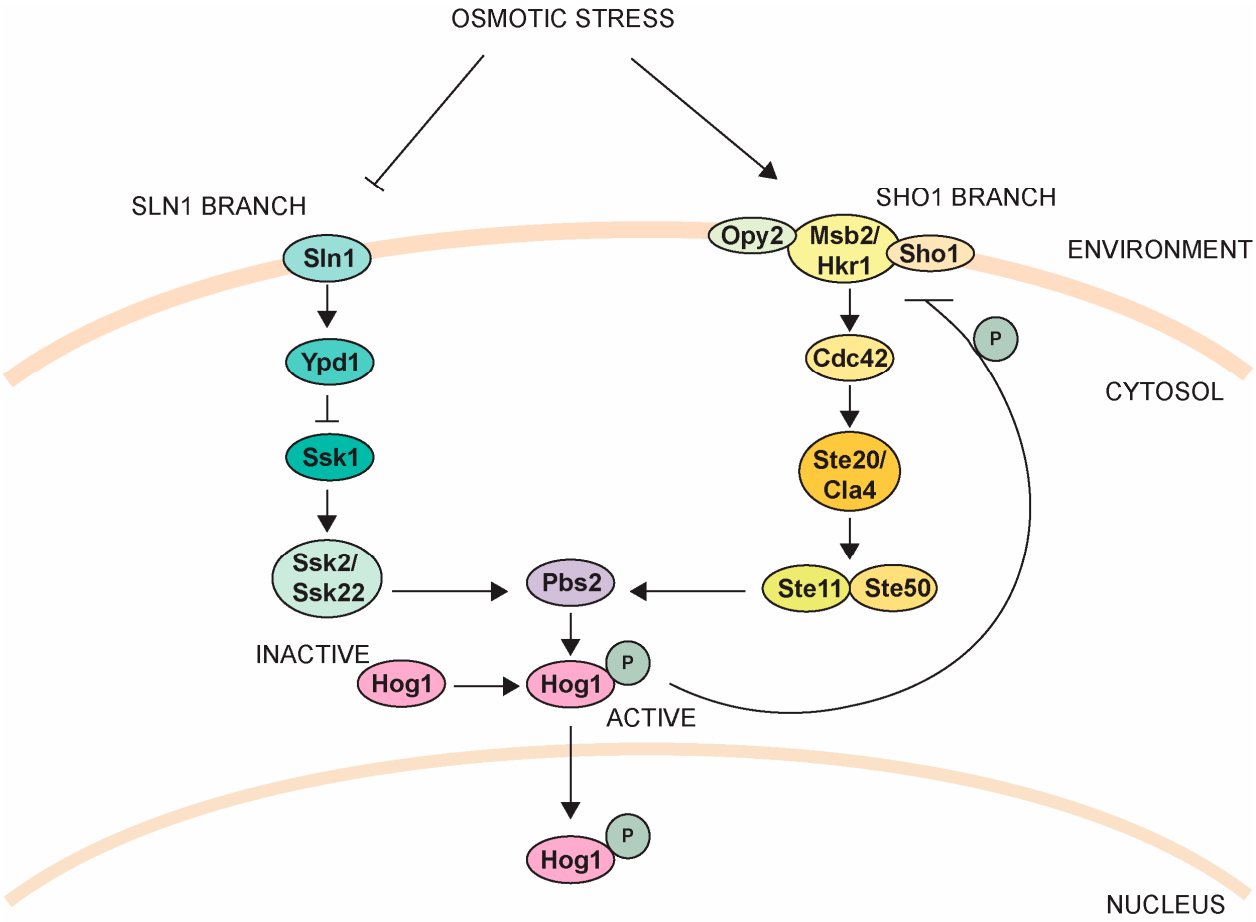

Figure 4. The high osmolarity glycerol pathway. See text for details [103].

4.4. Cell Cycle Regulation by PKA, Snf1, and HOG Pathways

The cell cycle is closely coordinated with the response to nutrients and stressors. During optimal conditions, the metabolism of nutrients provides the cell with basic resources to support DNA synthesis, rapid changes in gene expression, and mass accumulation. There are several checkpoints throughout the cell cycle to prevent progression if resources are unavailable or in the event of extreme stress in which cells often arrest. With their broad roles in regulating cellular physiology in response to nutrients and stress, it is not surprising that the PKA, Snf1, and HOG pathways contribute to cell cycle regulation.

While PKA and Snf1 have opposing roles in carbon signaling, they both exert positive control over the growth and division. PKA induces the expression of ribosomal protein genes and increases their translation [49,99,215,216]. This is hypothesized to affect the critical size a cell must reach before commitment to the cell cycle [215,217–223]. Snf1 has been reported to localize to the bud neck during mitosis, promote a proper mitotic spindle arrangement, and regulate the expression of G1-specific genes [224–228]. As we continue to obtain a better understanding of these two pathways, it is very likely that more detailed roles for PKA and Snf1 in cell cycle regulation will be uncovered.

Since stress can have dramatic negative effects on a cycling cell, Hog1 regulates arrest at several stages throughout the cell cycle. Hog1 can cause transient cell cycle arrest if it is activated for a short period of time or can lead the cell to apoptosis if the stress is sustained for an extended time [103,187,194,229,230]. Just as Hog1 modulates physiology via multiple mechanisms in response to stress, it also initiates cell cycle arrest by several methods: First, Hog1 delays the expression of cell phase-specific transcripts to prevent progression. Second,

Hog1 directly phosphorylates cell cycle regulatory proteins to modulate their activity, thus preventing progression [231–240]. Thus, proper Hog1 activity to promote cell cycle arrest in response to stress is crucial for cell survival.

5. Future Prospects

Much remains to be understood in terms of how cells normally integrate signaling pathways to control cellular systems and, in turn, how to modulate that integration for desired engineering solutions. The engineering of anaerobic xylose fermentation in *S. cerevisiae* showcases the importance of cellular rewiring but also highlights the challenges ahead for directed engineering. For example, much of our knowledge of the cellular rewiring that enables anaerobic xylose fermentation was discovered by studying mutations that emerged through the laboratory evolution of novel metabolic traits. As the field learns more about how cells have naturally evolved to integrate many signaling systems, the ability to engineer those outcomes for industrial use will also advance.

6. Conclusions

Recent work on engineering yeast for xylose fermentation has pointed to the importance of global signaling pathway integration. Research from our lab and others found that modulating the activity of the PKA, Snf1, and Hog1 pathways is required for efficient xylose fermentation, in addition to minimal genetic engineering with xylose metabolic genes. While this review summarized where xylose fermentation in yeast currently stands, it is evident there still remains much to uncover about the interconnectedness of the PKA, Snf1, and Hog1 pathways and how balancing their activity levels impacts growth, metabolism, and stress defense under industrial growth conditions.

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References

1. Cravens, A.; Payne, J.; Smolke, C.D. Synthetic biology strategies for microbial biosynthesis of plant natural products. *Nat. Commun.* **2019**, *10*, 2142. Available online: https://www.nature.com/articles/s41467-019-09848-w (accessed on 14 February 2023). [CrossRef]
2. Money, N.P. The Rise of Yeast: How the Sugar Fungus Shaped Civilization. 2018, p. 210. Available online: https://global.oup.com/academic/product/the-rise-of-yeast-9780198749707 (accessed on 17 February 2023).
3. Samuel, D. Investigation of Ancient Egyptian Baking and Brewing Methods by Correlative Microscopy. *Science* **1996**, *273*, 488–490. Available online: https://pubmed.ncbi.nlm.nih.gov/8662535/ (accessed on 17 February 2023). [CrossRef] [PubMed]

4. Nielsen, J. Yeast Systems Biology: Model Organism and Cell Factory. *Biotechnol. J.* **2019**, *14*, 1800421. Available online: https://onlinelibrary.wiley.com/doi/full/10.1002/biot.201800421 (accessed on 14 February 2023). [CrossRef] [PubMed]
5. Schindler, D. Genetic Engineering and Synthetic Genomics in Yeast to Understand Life and Boost Biotechnology. *Bioengineering* **2020**, *7*, 137. Available online: https://www.mdpi.com/2306-5354/7/4/137/htm (accessed on 14 February 2023). [CrossRef] [PubMed]
6. Ding, J.; Huang, X.; Zhang, L.; Zhao, N.; Yang, D.; Zhang, K. Tolerance and stress response to ethanol in the yeast *Saccharomyces cerevisiae*. *Appl. Microbiol. Biotechnol.* **2009**, *85*, 253–263. Available online: https://link.springer.com/article/10.1007/s00253-009-2223-1 (accessed on 20 February 2023). [CrossRef]
7. Liu, J.; Wang, X.; Dai, G.; Zhang, Y.; Bian, X. Microbial chassis engineering drives heterologous production of complex secondary metabolites. *Biotechnol. Adv.* **2022**, *59*, 107966. [CrossRef]
8. Zhang, C.; Ottenheim, C.; Weingarten, M.; Ji, L.H. Microbial Utilization of Next-Generation Feedstocks for the Biomanufacturing of Value-Added Chemicals and Food Ingredients. *Front. Bioeng. Biotechnol.* **2022**, *10*, 486. [CrossRef]
9. Shah, A.M.; Yang, W.; Mohamed, H.; Zhang, Y.; Song, Y. Microbes: A Hidden Treasure of Polyunsaturated Fatty Acids. *Front. Nutr.* **2022**, *9*, 415. [CrossRef]
10. Joshi, S.; Mishra, S.D. Recent advances in biofuel production through metabolic engineering. *Bioresour. Technol.* **2022**, *352*, 127037. [CrossRef]
11. Lau, M.W.; Gunawan, C.; Dale, B.E. The impacts of pretreatment on the fermentability of pretreated lignocellulosic biomass: A comparative evaluation between ammonia fiber expansion and dilute acid pretreatment. *Biotechnol. Biofuels* **2009**, *2*, 30. Available online: https://link.springer.com/articles/10.1186/1754-6834-2-30 (accessed on 18 February 2023). [CrossRef]
12. Singh, K.K.; Rasmussen, A.K.; Lene, A.; Rasmussen, J. Genome-Wide Analysis of Signal Transducers and Regulators of Mitochondrial Dysfunction in *Saccharomyces cerevisiae*. *Ann. N. Y. Acad. Sci.* **2004**, *1011*, 284–298. Available online: http://mips.gsf.de (accessed on 11 June 2020). [CrossRef] [PubMed]
13. Liu, Z.L. Molecular mechanisms of yeast tolerance and in situ detoxification of lignocellulose hydrolysates. *Appl. Microbiol. Biotechnol.* **2011**, *90*, 809–825. Available online: https://link.springer.com/article/10.1007/s00253-011-3167-9 (accessed on 18 February 2023). [CrossRef]
14. Cunha, J.T.; Romaní, A.; Costa, C.E.; Sá-Correia, I.; Domingues, L. Molecular and physiological basis of *Saccharomyces cerevisiae* tolerance to adverse lignocellulose-based process conditions. *Appl. Microbiol. Biotechnol.* **2018**, *103*, 159–175. Available online: https://link.springer.com/article/10.1007/s00253-018-9478-3 (accessed on 18 February 2023). [CrossRef] [PubMed]
15. Fletcher, E.; Baetz, K. Multi-Faceted Systems Biology Approaches Present a Cellular Landscape of Phenolic Compound Inhibition in *Saccharomyces cerevisiae*. *Front. Bioeng. Biotechnol.* **2020**, *8*, 1126. [CrossRef] [PubMed]
16. Baruah, J.; Nath, B.K.; Sharma, R.; Kumar, S.; Deka, R.C.; Baruah, D.C.; Kalita, E. Recent trends in the pretreatment of lignocellulosic biomass for value-added products. *Front. Energy Res.* **2018**, *6*, 141. [CrossRef]
17. Luterbacher, J.S.; Rand, J.M.; Alonso, D.M.; Han, J.; Youngquist, J.T.; Maravelias, C.T.; Pfleger, B.F.; Dumesic, J.A. Nonenzymatic sugar production from biomass using biomass-derived γ-valerolactone. *Science* **2014**, *343*, 277–280. Available online: https://www.science.org/doi/10.1126/science.1246748 (accessed on 18 February 2023). [CrossRef]
18. Hou, Q.; Ju, M.; Li, W.; Liu, L.; Chen, Y.; Yang, Q. Pretreatment of Lignocellulosic Biomass with Ionic Liquids and Ionic Liquid-Based Solvent Systems. *Molecules* **2017**, *22*, 490. Available online: https://www.mdpi.com/1420-3049/22/3/490/htm (accessed on 18 February 2023). [CrossRef]
19. Ouellet, M.; Datta, S.; Dibble, D.C.; Tamrakar, P.R.; Benke, P.I.; Li, C.; Singh, S.; Sale, K.L.; Adams, P.D.; Keasling, J.D.; et al. Impact of ionic liquid pretreated plant biomass on *Saccharomyces cerevisiae* growth and biofuel production. *Green. Chem.* **2011**, *13*, 2743–2749. Available online: https://pubs.rsc.org/en/content/articlehtml/2011/gc/c1gc15327g (accessed on 18 February 2023). [CrossRef]
20. Vanacloig-Pedros, E.; Fisher, K.J.; Liu, L.; Debrauske, D.J.; Young, M.K.M.; Place, M.; Hittinger, C.T.; Sato, T.K.; Gasch, A.P. Comparative chemical genomic profiling across plant-based hydrolysate toxins reveals widespread antagonism in fitness contributions. *FEMS Yeast Res.* **2022**, *22*, foac036. Available online: https://academic.oup.com/femsyr/article/22/1/foac036/6650360 (accessed on 18 February 2023). [CrossRef]
21. Piotrowski, J.S.; Zhang, Y.; Bates, D.M.; Keating, D.H.; Sato, T.K.; Ong, I.M.; Landick, R. Death by a thousand cuts: The challenges and diverse landscape of lignocellulosic hydrolysate inhibitors. *Front. Microbiol.* **2014**, *5*, 90. Available online: http://journal.frontiersin.org/article/10.3389/fmicb.2014.00090/abstract (accessed on 24 January 2019). [CrossRef]
22. Palmqvist, E.; Hahn-Hägerdal, B. Fermentation of lignocellulosic hydrolysates. II: Inhibitors and mechanisms of inhibition. *Bioresour. Technol.* **2000**, *74*, 25–33. [CrossRef]
23. Almeida, J.R.M.; Modig, T.; Petersson, A.; Hähn-Hägerdal, B.; Lidén, G.; Gorwa-Grauslund, M.F. Increased tolerance and conversion of inhibitors in lignocellulosic hydrolysates by *Saccharomyces cerevisiae*. *J. Chem. Technol. Biotechnol.* **2007**, *82*, 340–349. Available online: https://onlinelibrary.wiley.com/doi/full/10.1002/jctb.1676 (accessed on 18 February 2023). [CrossRef]
24. Chundawat, S.P.S.; Vismeh, R.; Sharma, L.N.; Humpula, J.F.; da Costa Sousa, L.; Chambliss, C.K.; Jones, A.D.; Balan, V.; Dale, B.E. Multifaceted characterization of cell wall decomposition products formed during ammonia fiber expansion (AFEX) and dilute acid based pretreatments. *Bioresour. Technol.* **2010**, *101*, 8429–8438. Available online: https://www.sciencedirect.com/science/article/pii/S0960852410010084 (accessed on 24 January 2019). [CrossRef]

25. Klinke, H.B.; Thomsen, A.B.; Ahring, B.K. Inhibition of ethanol-producing yeast and bacteria by degradation products produced during pre-treatment of biomass. *Appl. Microbiol. Biotechnol.* **2004**, *66*, 10–26. Available online: http://link.springer.com/10.1007/s00253-004-1642-2 (accessed on 24 January 2019). [CrossRef]
26. Bunnell, K.; Rich, A.; Luckett, C.; Wang, Y.J.; Martin, E.; Carrier, D.J. Plant maturity effects on the physicochemical properties and dilute acid hydrolysis of switchgrass (*Panicum virgatum*, L.) hemicelluloses. *ACS Sustain. Chem. Eng.* **2013**, *1*, 649–654. Available online: https://pubs.acs.org/doi/full/10.1021/sc4000175 (accessed on 18 February 2023). [CrossRef]
27. Jönsson, L.J.; Martín, C. Pretreatment of lignocellulose: Formation of inhibitory by-products and strategies for minimizing their effects. *Bioresour. Technol.* **2016**, *199*, 103–112. [CrossRef]
28. Ong, R.G.; Higbee, A.; Bottoms, S.; Dickinson, Q.; Xie, D.; Smith, S.A.; Serate, J.; Pohlmann, E.; Jones, A.D.; Coon, J.J.; et al. Inhibition of microbial biofuel production in drought-stressed switchgrass hydrolysate. *Biotechnol. Biofuels* **2016**, *9*, 237. Available online: https://link.springer.com/articles/10.1186/s13068-016-0657-0 (accessed on 18 February 2023). [CrossRef]
29. Wehrs, M.; Thompson, M.G.; Banerjee, D.; Prahl, J.P.; Morella, N.M.; Barcelos, C.A.; Moon, J.; Costello, Z.; Keasling, J.D.; Shih, P.M.; et al. Investigation of Bar-seq as a method to study population dynamics of *Saccharomyces cerevisiae* deletion library during bioreactor cultivation. *Microb. Cell Fact.* **2020**, *19*, 167. Available online: https://link.springer.com/articles/10.1186/s12934-020-01423-z (accessed on 18 February 2023). [CrossRef] [PubMed]
30. Brauer, M.J.; Huttenhower, C.; Airoldi, E.M.; Rosenstein, R.; Matese, J.C.; Gresham, D.; Boer, V.M.; Troyanskaya, O.G.; Botstein, D. Coordination of growth rate, cell cycle, stress response, and metabolic activity in yeast. *Mol. Biol. Cell* **2008**, *19*, 352–367. Available online: https://www.molbiolcell.org/doi/10.1091/mbc.e07-08-0779 (accessed on 8 September 2022). [CrossRef] [PubMed]
31. Gibney, P.A.; Lu, C.; Caudy, A.A.; Hess, D.C.; Botstein, D. Yeast metabolic and signaling genes are required for heat-shock survival and have little overlap with the heat-induced genes. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, E4393–E4402. Available online: https://pubmed.ncbi.nlm.nih.gov/24167267/ (accessed on 1 June 2023). [CrossRef] [PubMed]
32. Slavov, N.; Botstein, D. Coupling among growth rate response, metabolic cycle, and cell division cycle in yeast. *Mol. Biol. Cell* **2011**, *22*, 1997–2009. Available online: https://pubmed.ncbi.nlm.nih.gov/21525243/ (accessed on 1 June 2023). [CrossRef]
33. Chasman, D.; Ho, Y.; Berry, D.B.; Nemec, C.M.; MacGilvray, M.E.; Hose, J.; Merrill, A.E.; Lee, M.V.; Will, J.L.; Coon, J.J.; et al. Pathway connectivity and signaling coordination in the yeast stress-activated signaling network. *Mol. Syst. Biol.* **2014**, *10*, 759. Available online: https://onlinelibrary.wiley.com/doi/abs/10.15252/msb.20145120 (accessed on 14 April 2020). [CrossRef] [PubMed]
34. Ho, Y.H.; Shishkova, E.; Hose, J.; Coon, J.J.; Gasch, A.P. Decoupling Yeast Cell Division and Stress Defense Implicates mRNA Repression in Translational Reallocation during Stress. *Curr. Biol.* **2018**, *28*, 2673–2680.e4. [CrossRef] [PubMed]
35. Ho, Y.-H.; Gasch, A.P. Exploiting the yeast stress-activated signaling network to inform on stress biology and disease signaling. *Curr. Genet.* **2015**, *61*, 503–511. Available online: http://link.springer.com/10.1007/s00294-015-0491-0 (accessed on 24 January 2019). [CrossRef] [PubMed]
36. Lu, C.; Brauer, M.J.; Botstein, D. Slow growth induces heat-shock resistance in normal and respiratory-deficient yeast. *Mol. Biol. Cell* **2009**, *20*, 891–903. Available online: https://pubmed.ncbi.nlm.nih.gov/19056679/ (accessed on 1 June 2023). [CrossRef]
37. Gasch, A.P.; Spellman, P.T.; Kao, C.M.; Carmel-Harel, O.; Eisen, M.B.; Storz, G.; Botstein, D.; Brown, P.O. Genomic Expression Programs in the Response of Yeast Cells to Environmental Changes. *Mol. Biol. Cell* **2000**, *11*, 4241–4257. Available online: http://www.molbiolcell.org/doi/10.1091/mbc.11.12.4241 (accessed on 19 March 2019). [CrossRef]
38. Gasch, A.P. Yeast genomic expression studies using DNA microarrays. *Methods Enzymol.* **2002**, *350*, 393–414.
39. Pascual-Ahuir, A.; Manzanares-Estreder, S.; Timón-Gómez, A.; Proft, M. Ask yeast how to burn your fats: Lessons learned from the metabolic adaptation to salt stress. *Curr. Genet.* **2018**, *64*, 63–69. Available online: https://pubmed.ncbi.nlm.nih.gov/28631015/ (accessed on 1 June 2023). [CrossRef]
40. Martínez-Montañés, F.; Pascual-Ahuir, A.; Proft, M. Toward a genomic view of the gene expression program regulated by osmostress in yeast. *OMICS* **2010**, *14*, 619–627. Available online: https://pubmed.ncbi.nlm.nih.gov/20726780/ (accessed on 1 June 2023). [CrossRef]
41. Estruch, F.; Carlson, M. Two homologous zinc finger genes identified by multicopy suppression in a SNF1 protein kinase mutant of *Saccharomyces cerevisiae*. *Mol. Cell Biol.* **1993**, *13*, 3872–3881. Available online: https://pubmed.ncbi.nlm.nih.gov/8321194/ (accessed on 1 June 2023).
42. Schmitt, A.P.; Mcentee, K. Msn2p, a zinc finger DNA-binding protein, is the transcriptional activator of the multistress response in *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 5777–5782. Available online: https://pubmed.ncbi.nlm.nih.gov/8650168/ (accessed on 1 June 2023). [CrossRef] [PubMed]
43. Martínez-Pastor, M.T.; Marchler, G.; Schüller, C.; Marchler-Bauer, A.; Ruis, H.; Estruch, F. The *Saccharomyces cerevisiae* zinc finger proteins Msn2p and Msn4p are required for transcriptional induction through the stress response element (STRE). *EMBO J.* **1996**, *15*, 2227–2235. Available online: http://www.ncbi.nlm.nih.gov/pubmed/8641288 (accessed on 14 March 2019). [CrossRef] [PubMed]
44. Castrillo, J.I.; Zeef, L.A.; Hoyle, D.C.; Zhang, N.; Hayes, A.; Gardner, D.C.J.; Cornell, M.J.; Petty, J.; Hakes, L.; Wardleworth, L.; et al. Growth control of the eukaryote cell: A systems biology study in yeast. *J. Biol.* **2007**, *6*, 1–25. Available online: https://jbiol.biomedcentral.com/articles/10.1186/jbiol54 (accessed on 16 June 2022). [CrossRef] [PubMed]
45. Regenberg, B.; Grotkjær, T.; Winther, O.; Fausbøll, A.; Åkesson, M.; Bro, C.; Hansen, L.K.; Brunak, S.; Nielsen, J. Growth-rate regulated genes have profound impact on interpretation of transcriptome profiling in *Saccharomyces cerevisiae*. *Genome Biol.* **2006**, *7*, R107. Available online: https://genomebiology.biomedcentral.com/articles/10.1186/gb-2006-7-11-r107 (accessed on 8 September 2022). [CrossRef]

46. Airoldi, E.M.; Huttenhower, C.; Gresham, D.; Lu, C.; Caudy, A.A.; Dunham, M.J.; Broach, J.R.; Botstein, D.; Troyanskaya, O.G. Predicting Cellular Growth from Gene Expression Signatures. *PLoS Comput. Biol.* **2009**, *5*, e1000257. Available online: https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1000257 (accessed on 8 September 2022). [CrossRef]
47. Lee, M.V.; Topper, S.E.; Hubler, S.L.; Hose, J.; Wenger, C.D.; Coon, J.J.; Gasch, A.P. A dynamic model of proteome changes reveals new roles for transcript alteration in yeast. *Mol. Syst. Biol.* **2011**, *7*, 514. Available online: https://pubmed.ncbi.nlm.nih.gov/21772262/ (accessed on 1 June 2023). [CrossRef]
48. Bergen, A.C.; Kocik, R.A.; Hose, J.; McClean, M.N.; Gasch, A.P. Modeling single-cell phenotypes links yeast stress acclimation to transcriptional repression and pre-stress cellular states. *Elife* **2022**, *11*, e82017. Available online: https://pubmed.ncbi.nlm.nih.gov/36350693/ (accessed on 1 June 2023). [CrossRef]
49. Görner, W.; Durchschlag, E.; Martinez-Pastor, M.T.; Estruch, F.; Ammerer, G.; Hamilton, B.; Ruis, H.; Schüller, C. Nuclear localization of the C_2H_2 zinc finger protein Msn2p is regulated by stress and protein kinase A activity. *Genes. Dev.* **1998**, *12*, 586–597. Available online: http://www.ncbi.nlm.nih.gov/pubmed/9472026 (accessed on 14 March 2019). [CrossRef]
50. Lippman, S.I.; Broach, J.R. Protein kinase A and TORC1 activate genes for ribosomal biogenesis by inactivating repressors encoded by Dot6 and its homolog Tod6. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 19928–19933. Available online: http://www.ncbi.nlm.nih.gov/pubmed/19901341 (accessed on 25 March 2019). [CrossRef]
51. Pokholok, D.K.; Zeitlinger, J.; Hannett, N.M.; Reynolds, D.B.; Young, R.A. Activated signal transduction kinases frequently occupy target genes. *Science* **2006**, *313*, 533–536. Available online: http://www.ncbi.nlm.nih.gov/pubmed/16873666 (accessed on 13 February 2019). [CrossRef]
52. Pelechano, V.; Jimeno-González, S.; Rodríguez-Gil, A.; García-Martínez, J.; Pérez-Ortín, J.E.; Chávez, S. Regulon-Specific Control of Transcription Elongation across the Yeast Genome. *PLoS Genet.* **2009**, *5*, e1000614. [CrossRef] [PubMed]
53. Baccarini, L.; Martínez-Montañés, F.; Rossi, S.; Proft, M.; Portela, P. PKA-chromatin association at stress responsive target genes from *Saccharomyces cerevisiae*. *Biochim. Biophys. Acta—Gene Regul. Mech.* **2015**, *1849*, 1329–1339. Available online: https://www.sciencedirect.com/science/article/pii/S1874939915001935?via%3Dihub (accessed on 29 January 2019). [CrossRef] [PubMed]
54. Chang, Y.-W.; Howard, S.C.; Herman, P.K. The Ras/PKA Signaling Pathway Directly Targets the Srb9 Protein, a Component of the General RNA Polymerase II Transcription Apparatus. *Mol. Cell* **2004**, *15*, 107–116. Available online: https://www.sciencedirect.com/science/article/pii/S1097276504003077?via%3Dihub (accessed on 28 March 2019). [CrossRef]
55. De Wever, V.; Reiter, W.; Ballarini, A.; Ammerer, G.; Brocard, C. A dual role for PP1 in shaping the Msn2-dependent transcriptional response to glucose starvation. *EMBO J.* **2005**, *24*, 4115–4123. Available online: https://pubmed.ncbi.nlm.nih.gov/16281053/ (accessed on 25 January 2023). [CrossRef] [PubMed]
56. Li, L.; Kaplan, J.; Ward, D.M. The glucose sensor Snf1 and the transcription factors Msn2 and Msn4 regulate transcription of the vacuolar iron importer gene CCC1 and iron resistance in yeast. *J. Biol. Chem.* **2017**, *292*, 15577–15586. Available online: https://pubmed.ncbi.nlm.nih.gov/28760824/ (accessed on 25 January 2023). [CrossRef] [PubMed]
57. Bodenmiller, B.; Wanka, S.; Kraft, C.; Urban, J.; Campbell, D.; Pedrioli, P.G.; Gerrits, B.; Picotti, P.; Lam, H.; Vitek, O.; et al. Phosphoproteomic analysis reveals interconnected system-wide responses to perturbations of kinases and phosphatases in yeast. *Sci. Signal* **2010**, *3*, rs4. Available online: https://pubmed.ncbi.nlm.nih.gov/21177495/ (accessed on 1 June 2023). [CrossRef]
58. Ho, N.W.; Chen, Z.; Brainard, A.P.; Sedlak, M. Successful design and development of genetically engineered Saccharomyces yeasts for effective cofermentation of glucose and xylose from cellulosic biomass to fuel ethanol. *Adv. Biochem. Eng. Biotechnol.* **1999**, *65*, 163–192. Available online: https://pubmed.ncbi.nlm.nih.gov/10533435/ (accessed on 1 June 2023).
59. Jagger, A. Biofuels for transport in 2050. *Biofuels Bioprod Biorefining* **2011**, *5*, 481–485. Available online: https://onlinelibrary.wiley.com/doi/full/10.1002/bbb.330 (accessed on 17 February 2023). [CrossRef]
60. Eisentraut, A. Sustainable Production of Second-Generation Biofuels: Potential and Perspectives in Major Economies and Developing Countries | IEA Energy Papers | OECD iLibrary IEA Energy Papers. 2010. Available online: https://www.oecd-ilibrary.org/energy/sustainable-production-of-second-generation-biofuels_5kmh3njpt6r0-en (accessed on 17 February 2023).
61. Sims, R.; Taylor, M.; Saddler, J.; Mabee, W. FROM 1st-TO 2nd-GENERATION BIOFUEL TECHNOLOGIES An Overview of Current Industry and RD&D Activities. Available online: www.ieabioenergy.com (accessed on 17 February 2023).
62. Buijs, N.A.; Siewers, V.; Nielsen, J. Advanced biofuel production by the yeast *Saccharomyces cerevisiae*. *Curr. Opin. Chem. Biol.* **2013**, *17*, 480–488. [CrossRef]
63. Jin, C.; Yao, M.; Liu, H.; Lee, C.F.F.; Ji, J. Progress in the production and application of n-butanol as a biofuel. *Renew. Sustain. Energy Rev.* **2011**, *15*, 4080–4106. [CrossRef]
64. Azambuja, S.P.H.; Goldbeck, R. Butanol production by *Saccharomyces cerevisiae*: Perspectives, strategies and challenges. *World J. Microbiol. Biotechnol.* **2020**, *36*, 48. Available online: https://link.springer.com/article/10.1007/s11274-020-02828-z (accessed on 17 February 2023). [CrossRef] [PubMed]
65. Sakuragi, H.; Morisaka, H.; Kuroda, K.; Ueda, M. Enhanced butanol production by eukaryotic *Saccharomyces cerevisiae* engineered to contain an improved pathway. *Biosci. Biotechnol. Biochem.* **2015**, *79*, 314–320. Available online: https://academic.oup.com/bbb/article/79/2/314/5939446 (accessed on 17 February 2023). [CrossRef] [PubMed]
66. Choi, Y.J.; Lee, J.; Jang, Y.S.; Lee, S.Y. Metabolic engineering of microorganisms for the production of higher alcohols. *MBio* **2014**, *5*. Available online: https://journals.asm.org/doi/10.1128/mBio.01524-14 (accessed on 17 February 2023). [CrossRef] [PubMed]
67. Si, T.; Luo, Y.; Xiao, H.; Zhao, H. Utilizing an endogenous pathway for 1-butanol production in *Saccharomyces cerevisiae*. *Metab. Eng.* **2014**, *22*, 60–68. [CrossRef] [PubMed]

68. Swidah, R.; Wang, H.; Reid, P.J.; Ahmed, H.Z.; Pisanelli, A.M.; Persaud, K.C.; Grant, C.M.; Ashe, M.P. Butanol production in S. cerevisiae via a synthetic ABE pathway is enhanced by specific metabolic engineering and butanol resistance. *Biotechnol. Biofuels* **2015**, *8*, 97. [CrossRef]
69. Schadeweg, V.; Boles, E. N-Butanol production in *Saccharomyces cerevisiae* is limited by the availability of coenzyme A and cytosolic acetyl-CoA. *Biotechnol. Biofuels* **2016**, *9*, 44. Available online: https://biotechnologyforbiofuels.biomedcentral.com/articles/10.1186/s13068-016-0456-7 (accessed on 17 February 2023). [CrossRef]
70. Krivoruchko, A.; Serrano-Amatriain, C.; Chen, Y.; Siewers, V.; Nielsen, J. Improving biobutanol production in engineered *Saccharomyces cerevisiae* by manipulation of acetyl-CoA metabolism. *J. Ind. Microbiol. Biotechnol.* **2013**, *40*, 1051–1056. Available online: https://pubmed.ncbi.nlm.nih.gov/23760499/ (accessed on 17 February 2023). [CrossRef]
71. Schadeweg, V.; Boles, E. Increasing n-butanol production with *Saccharomyces cerevisiae* by optimizing acetyl-CoA synthesis, NADH levels and trans-2-enoyl-CoA reductase expression. *Biotechnol. Biofuels* **2016**, *9*, 257. Available online: https://biotechnologyforbiofuels.biomedcentral.com/articles/10.1186/s13068-016-0673-0 (accessed on 17 February 2023). [CrossRef]
72. Gambacorta, F.V.; Wagner, E.R.; Jacobson, T.B.; Tremaine, M.; Muehlbauer, L.K.; McGee, M.A.; Baerwald, J.J.; Wrobel, R.L.; Wolters, J.F.; Place, M.; et al. Comparative functional genomics identifies an iron-limited bottleneck in a *Saccharomyces cerevisiae* strain with a cytosolic-localized isobutanol pathway. *Synth. Syst. Biotechnol.* **2022**, *7*, 738–749. Available online: https://pubmed.ncbi.nlm.nih.gov/35387233/ (accessed on 17 February 2023). [CrossRef]
73. Kuroda, K.; Ueda, M. Cellular and molecular engineering of yeast *Saccharomyces cerevisiae* for advanced biobutanol production. *FEMS Microbiol. Lett.* **2016**, *363*, 247. Available online: https://academic.oup.com/femsle/article/363/3/fnv247/2594551 (accessed on 17 February 2023). [CrossRef]
74. Hong, K.K.; Nielsen, J. Metabolic engineering of *Saccharomyces cerevisiae*: A key cell factory platform for future biorefineries. *Cell Mol. Life Sci.* **2012**, *69*, 2671–2690. Available online: https://link.springer.com/article/10.1007/s00018-012-0945-1 (accessed on 17 February 2023). [CrossRef] [PubMed]
75. Generoso, W.C.; Schadeweg, V.; Oreb, M.; Boles, E. Metabolic engineering of *Saccharomyces cerevisiae* for production of butanol isomers. *Curr. Opin. Biotechnol.* **2015**, *33*, 1–7. [CrossRef] [PubMed]
76. Steen, E.J.; Chan, R.; Prasad, N.; Myers, S.; Petzold, C.J.; Redding, A.; Ouellet, M.; Keasling, J.D. Metabolic engineering of *Saccharomyces cerevisiae* for the production of n-butanol. *Microb. Cell Fact.* **2008**, *7*, 36. Available online: https://microbialcellfactories.biomedcentral.com/articles/10.1186/1475-2859-7-36 (accessed on 17 February 2023). [CrossRef] [PubMed]
77. Lian, J.; Si, T.; Nair, N.U.; Zhao, H. Design and construction of acetyl-CoA overproducing *Saccharomyces cerevisiae* strains. *Metab. Eng.* **2014**, *24*, 750–760. Available online: https://pubmed.ncbi.nlm.nih.gov/24853351/ (accessed on 17 February 2023). [CrossRef]
78. Kim, S.R.; Ha, S.-J.; Wei, N.; Oh, E.J.; Jin, Y.-S. Simultaneous co-fermentation of mixed sugars: A promising strategy for producing cellulosic ethanol. *Trends Biotechnol.* **2012**, *30*, 274–282. Available online: https://www.sciencedirect.com/science/article/pii/S0167779912000157 (accessed on 24 January 2019). [CrossRef]
79. Lee, J.W.; Yook, S.; Koh, H.; Rao, C.V.; Jin, Y.S. Engineering xylose metabolism in yeasts to produce biofuels and chemicals. *Curr. Opin. Biotechnol.* **2021**, *67*, 15–25. [CrossRef]
80. Wohlbach, D.J.; Kuo, A.; Sato, T.K.; Potts, K.M.; Salamov, A.A.; LaButti, K.M.; Sun, H.; Clum, A.; Pangilian, J.L.; Lindquist, E.A.; et al. Comparative genomics of xylose-fermenting fungi for enhanced biofuel production. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 13212–13217. Available online: https://pubmed.ncbi.nlm.nih.gov/21788494/ (accessed on 18 February 2023). [CrossRef]
81. Harner, N.K.; Wen, X.; Bajwa, P.K.; Austin, G.D.; Ho, C.Y.; Habash, M.B.; Trevors, J.T.; Lee, H. Genetic improvement of native xylose-fermenting yeasts for ethanol production. *J. Ind. Microbiol. Biotechnol.* **2015**, *42*, 1–20. Available online: https://pubmed.ncbi.nlm.nih.gov/25404205/ (accessed on 16 May 2023). [CrossRef]
82. Trichez, D.; Steindorff, A.S.; de Morais Júnior, W.G.; Vilela, N.; Bergmann, J.C.; Formighieri, E.F.; Gonçalves, S.B.; de Almeida, J.R.M. Identification of traits to improve co-assimilation of glucose and xylose by adaptive evolution of Spathaspora passalidarum and Scheffersomyces stipitis yeasts. *Appl. Microbiol. Biotechnol.* **2023**, *107*, 1143–1157. Available online: https://pubmed.ncbi.nlm.nih.gov/36625916/ (accessed on 16 May 2023). [CrossRef]
83. Kim, S.R.; Skerker, J.M.; Kang, W.; Lesmana, A.; Wei, N.; Arkin, A.P.; Jin, Y. Rational and Evolutionary Engineering Approaches Uncover a Small Set of Genetic Changes Efficient for Rapid Xylose Fermentation in *Saccharomyces cerevisiae*. *PLoS ONE* **2013**, *8*, e57048. [CrossRef]
84. Kwak, S.; Jin, Y.S. Production of fuels and chemicals from xylose by engineered *Saccharomyces cerevisiae*: A review and perspective. *Microb. Cell Fact.* **2017**, *16*, 82. Available online: https://pubmed.ncbi.nlm.nih.gov/28494761/ (accessed on 1 June 2023). [CrossRef]
85. Kuyper, M.; Harhangi, H.; Stave, A.; Winkler, A.; Jetten, M.; Delaat, W.; den Ridder, J.J.J.; Op den Camp, H.J.M.; van Dijken, J.P.; Pronk, J.Y. High-level functional expression of a fungal xylose isomerase: The key to efficient ethanolic fermentation of xylose by *Saccharomyces cerevisiae* ? *FEMS Yeast Res.* **2003**, *4*, 69–78. Available online: https://academic.oup.com/femsyr/article-lookup/doi/10.1016/S1567-1356(03)00141-7 (accessed on 24 January 2019). [CrossRef] [PubMed]
86. Kuyper, M.; Hartog, M.; Toirkens, M.; Almering, M.; Winkler, A.; Vandijken, J.; Pronk, J.T. Metabolic engineering of a xylose-isomerase-expressing strain for rapid anaerobic xylose fermentation. *FEMS Yeast Res.* **2005**, *5*, 399–409. Available online: https://academic.oup.com/femsyr/article-lookup/doi/10.1016/j.femsyr.2004.09.010 (accessed on 24 January 2019). [CrossRef] [PubMed]

87. Parreiras, L.S.; Breuer, R.J.; Avanasi Narasimhan, R.; Higbee, A.J.; La Reau, A.; Tremaine, M.; Qin, L.; Willis, L.B.; Bice, B.D.; Bonfert, B.L.; et al. Engineering and Two-Stage Evolution of a Lignocellulosic Hydrolysate-Tolerant *Saccharomyces cerevisiae* Strain for Anaerobic Fermentation of Xylose from AFEX Pretreated Corn Stover. *PLoS ONE* **2014**, *9*, e107499. [CrossRef] [PubMed]
88. Kim, S.R.; Park, Y.C.; Jin, Y.S.; Seo, J.H. Strain engineering of *Saccharomyces cerevisiae* for enhanced xylose metabolism. *Biotechnol. Adv.* **2013**, *31*, 851–861. [CrossRef]
89. Osiro, K.O.; Brink, D.P.; Borgström, C.; Wasserstrom, L.; Carlquist, M.; Gorwa-Grauslund, M.F. Assessing the effect of d-xylose on the sugar signaling pathways of *Saccharomyces cerevisiae* in strains engineered for xylose transport and assimilation. *FEMS Yeast Res.* **2018**, *18*, 1. Available online: https://academic.oup.com/femsyr/article/doi/10.1093/femsyr/fox096/4791530 (accessed on 3 April 2019). [CrossRef]
90. Osiro, K.O.; Borgström, C.; Brink, D.P.; Fjölnisdóttir, B.L.; Gorwa-Grauslund, M.F. Exploring the xylose paradox in *Saccharomyces cerevisiae* through in vivo sugar signalomics of targeted deletants. *Microb. Cell Fact.* **2019**, *18*, 88. Available online: https://microbialcellfactories.biomedcentral.com/articles/10.1186/s12934-019-1141-x (accessed on 3 September 2020). [CrossRef]
91. Endalur Gopinarayanan, V.; Nair, N.U. Pentose Metabolism in *Saccharomyces cerevisiae*: The Need to Engineer Global Regulatory Systems. *Biotechnol. J.* **2019**, *14*, 1800364. Available online: https://onlinelibrary.wiley.com/doi/full/10.1002/biot.201800364 (accessed on 17 February 2023). [CrossRef]
92. Wei, S.; Liu, Y.; Wu, M.; Ma, T.; Bai, X.; Hou, J.; Shen, Y.; Bao, X. Disruption of the transcription factors Thi2p and Nrm1p alleviates the post-glucose effect on xylose utilization in *Saccharomyces cerevisiae*. *Biotechnol. Biofuels* **2018**, *11*, 112. Available online: https://biotechnologyforbiofuels.biomedcentral.com/articles/10.1186/s13068-018-1112-1 (accessed on 17 February 2023). [CrossRef]
93. Wei, S.; Bai, P.; Liu, Y.; Yang, M.; Ma, J.; Hou, J.; Liu, W.; Bao, X.; Shen, Y. A Thi2p Regulatory Network Controls the Post-glucose Effect of Xylose Utilization in *Saccharomyces cerevisiae*. *Front. Microbiol.* **2019**, *10*, 1649. [CrossRef]
94. Wu, M.; Li, H.; Wei, S.; Wu, H.; Wu, X.; Bao, X.; Hou, J.; Liu, W.; Shen, Y. Simulating Extracellular Glucose Signals Enhances Xylose Metabolism in Recombinant *Saccharomyces cerevisiae*. *Microorganisms* **2020**, *8*, 100. Available online: https://www.mdpi.com/2076-2607/8/1/100 (accessed on 4 June 2020). [CrossRef] [PubMed]
95. Endalur Gopinarayanan, V.; Nair, N.U. A semi-synthetic regulon enables rapid growth of yeast on xylose. *Nat. Commun.* **2018**, *9*, 1233. Available online: https://www.nature.com/articles/s41467-018-03645-7 (accessed on 17 February 2023). [CrossRef]
96. Sato, T.K.; Tremaine, M.; Parreiras, L.S.; Hebert, A.S.; Myers, K.S.; Higbee, A.J.; Sardi, M.; McIlwain, S.J.; Ong, I.M.; Breuer, R.J.; et al. Directed Evolution Reveals Unexpected Epistatic Interactions That Alter Metabolic Regulation and Enable Anaerobic Xylose Use by *Saccharomyces cerevisiae*. *PLOS Genet.* **2016**, *12*, e1006372. [CrossRef]
97. dos Santos, L.V.; Carazzolle, M.F.; Nagamatsu, S.T.; Sampaio, N.M.V.; Almeida, L.D.; Pirolla, R.A.S.; Borelli, G.; Corrêa, T.L.R.; Argueso, J.L.; Pereira, G.A.G. Unraveling the genetic basis of xylose consumption in engineered *Saccharomyces cerevisiae* strains. *Sci. Rep.* **2016**, *6*, 38676. Available online: http://www.nature.com/articles/srep38676 (accessed on 24 January 2019). [CrossRef] [PubMed]
98. Myers, K.S.; Riley, N.M.; MacGilvray, M.E.; Sato, T.K.; McGee, M.; Heilberger, J.; Coon, J.J.; Gasch, A.P. Rewired cellular signaling coordinates sugar and hypoxic responses for anaerobic xylose fermentation in yeast. *PLoS Genet.* **2019**, *15*, e1008037. [CrossRef]
99. Conrad, M.; Schothorst, J.; Kankipati, H.N.; Van Zeebroeck, G.; Rubio-Texeira, M.; Thevelein, J.M. Nutrient sensing and signaling in the yeast *Saccharomyces cerevisiae*. *FEMS Microbiol. Rev.* **2014**, *38*, 254–299. Available online: https://academic.oup.com/femsre/article-lookup/doi/10.1111/1574-6976.12065 (accessed on 24 January 2019). [CrossRef]
100. Coccetti, P.; Nicastro, R.; Tripodi, F. Conventional and emerging roles of the energy sensor Snf1/AMPK in *Saccharomyces cerevisiae*. *Microb. Cell* **2018**, *5*, 482. [CrossRef]
101. Vallejo, M.C.; Mayinger, P. Delayed Turnover of Unphosphorylated Ssk1 during Carbon Stress Activates the Yeast Hog1 Map Kinase Pathway. *PLoS ONE* **2015**, *10*, e0137199. Available online: https://pubmed.ncbi.nlm.nih.gov/26340004/ (accessed on 31 May 2023). [CrossRef]
102. Piao, H.; Maclean Freed, J.; Mayinger, P. Metabolic Activation of the HOG MAP Kinase Pathway by Snf1/AMPK Regulates Lipid Signaling at the Golgi. *Traffic* **2012**, *13*, 1522–1531. Available online: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-0854.2012.01406.x (accessed on 17 February 2023). [CrossRef]
103. Saito, H.; Posas, F. Response to hyperosmotic stress. *Genetics* **2012**, *192*, 289–318. Available online: http://www.ncbi.nlm.nih.gov/pubmed/9383053 (accessed on 24 January 2019). [CrossRef]
104. Thevelein, J.M.; de Winde, J.H. Novel sensing mechanisms and targets for the cAMP-protein kinase A pathway in the yeast *Saccharomyces cerevisiae*. *Mol. Microbiol.* **1999**, *33*, 904–918. Available online: http://doi.wiley.com/10.1046/j.1365-2958.1999.01538.x (accessed on 24 January 2019). [CrossRef] [PubMed]
105. Santangelo, G.M. Glucose signaling in *Saccharomyces cerevisiae*. *Microbiol. Mol. Biol. Rev.* **2006**, *70*, 253–282. Available online: http://www.ncbi.nlm.nih.gov/pubmed/16524925 (accessed on 9 April 2019). [CrossRef] [PubMed]
106. Smets, B.; Ghillebert, R.; De Snijder, P.; Binda, M.; Swinnen, E.; De Virgilio, C.; Winderickx, J. Life in the midst of scarcity: Adaptations to nutrient availability in *Saccharomyces cerevisiae*. *Curr. Genet.* **2010**, *56*, 1–32. Available online: http://link.springer.com/10.1007/s00294-009-0287-1 (accessed on 1 April 2019). [CrossRef]
107. Schepers, W.; Van Zeebroeck, G.; Pinkse, M.; Verhaert, P.; Thevelein, J.M. In vivo phosphorylation of Ser21 and Ser83 during nutrient-induced activation of the yeast protein kinase A (PKA) target trehalase. *J. Biol. Chem.* **2012**, *287*, 44130–44142. Available online: http://www.ncbi.nlm.nih.gov/pubmed/23155055 (accessed on 24 January 2019). [CrossRef] [PubMed]

108. Dihazi, H.; Kessler, R.; Eschrich, K. Glucose-Induced Stimulation of the Ras-cAMP Pathway in Yeast Leads to Multiple Phosphorylations and Activation of 6-Phosphofructo-2-Kinase. 2003. Available online: https://pubs.acs.org/doi/abs/10.1021/bi034167r (accessed on 24 January 2019).
109. Portela, P.; Moreno, S.; Rossi, S. Characterization of yeast pyruvate kinase 1 as a protein kinase A substrate, and specificity of the phosphorylation site sequence in the whole protein. *Biochem. J.* **2006**, *396*, 117–126. Available online: http://www.ncbi.nlm.nih.gov/pubmed/16426231 (accessed on 1 April 2019). [CrossRef]
110. Cameroni, E.; Hulo, N.; Roosen, J.; Winderickx, J.; De Virgilio, C. The Novel Yeast PAS Kinase Rim15 Orchestrates G0-Associated Antioxidant Defense Mechanisms. *Cell Cycle* **2004**, *3*, 462–468. [CrossRef]
111. Toda, T.; Cameron, S.; Sass, P.; Zoller, M.; Scott, J.D.; McMullen, B.; Hurwitz, M.; Krebs, E.G.; Wigler, M. Cloning and characterization of BCY1, a locus encoding a regulatory subunit of the cyclic AMP-dependent protein kinase in *Saccharomyces cerevisiae*. *Mol. Cell Biol.* **1987**, *7*, 1371–1377. Available online: http://www.ncbi.nlm.nih.gov/pubmed/3037314 (accessed on 7 March 2019).
112. Toda, T.; Cameron, S.; Sass, P.; Zoller, M.; Wigler, M. Three different genes in *S. cerevisiae* encode the catalytic subunits of the cAMP-dependent protein kinase. *Cell* **1987**, *50*, 277–287. Available online: https://www.sciencedirect.com/science/article/pii/0092867487902236?via%3Dihub (accessed on 7 March 2019). [CrossRef]
113. Cannon, J.F.; Tatchell, K. Characterization of *Saccharomyces cerevisiae* genes encoding subunits of cyclic AMP-dependent protein kinase. *Mol. Cell Biol.* **1987**, *7*, 2653–2663. Available online: http://www.ncbi.nlm.nih.gov/pubmed/2823100 (accessed on 8 March 2019).
114. Matsumoto, K.; Uno, I.; Oshima, Y.; Ishikawa, T. Isolation and characterization of yeast mutants deficient in adenylate cyclase and cAMP-dependent protein kinase. *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 2355–2359. Available online: http://www.ncbi.nlm.nih.gov/pubmed/6285379 (accessed on 8 March 2019). [CrossRef]
115. Kataoka, T.; Broek, D.; Wigler, M. DNA sequence and characterization of the *S. cerevisiae* gene encoding adenylate cyclase. *Cell* **1985**, *43*, 493–505. [CrossRef] [PubMed]
116. Casperson, G.F.; Walker, N.; Bourne, H.R. Isolation of the gene encoding adenylate cyclase in *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5060–5063. Available online: https://pubmed.ncbi.nlm.nih.gov/2991907/ (accessed on 18 February 2023). [CrossRef] [PubMed]
117. Broach, J.R.; Deschenes, R.J. The Function of Ras Genes in *Saccharomyces cerevisiae*. *Adv. Cancer Res.* **1990**, *54*, 79–139. Available online: https://www.sciencedirect.com/science/article/pii/S0065230X0860809X?via%3Dihub (accessed on 7 March 2019).
118. Broek, D.; Toda, T.; Michaeli, T.; Levin, L.; Birchmeier, C.; Zoller, M.; Powers, S.; Wigler, M. The S. cerevisiae CDC25 gene product regulates the RAS/adenylate cyclase pathway. *Cell* **1987**, *48*, 789–799. Available online: https://pubmed.ncbi.nlm.nih.gov/3545497/ (accessed on 18 February 2023). [CrossRef]
119. Boy-Marcotte, E.; Ikonomi, P.; Jacquet, M. SDC25, a dispensable Ras guanine nucleotide exchange factor of *Saccharomyces cerevisiae* differs from CDC25 by its regulation. *Mol. Biol. Cell* **1996**, *7*, 529. [CrossRef] [PubMed]
120. Colombo, S.; Ronchetti, D.; Thevelein, J.M.; Winderickx, J.; Martegani, E. Activation state of the Ras2 protein and glucose-induced signaling in *Saccharomyces cerevisiae*. *J. Biol. Chem.* **2004**, *279*, 46715–46722. Available online: http://www.ncbi.nlm.nih.gov/pubmed/15339905 (accessed on 1 April 2019). [CrossRef]
121. Colombo, S.; Ma, P.; Cauwenberg, L.; Winderickx, J.; Crauwels, M.; Teunissen, A.; Nauwelaers, D.; de Winde, J.H.; Gorwa, M.F.; Colavizza, D.; et al. Involvement of distinct G-proteins, Gpa2 and Ras, in glucose- and intracellular acidification-induced cAMP signalling in the yeast *Saccharomyces cerevisiae*. *EMBO J.* **1998**, *17*, 3326–3341. Available online: https://pubmed.ncbi.nlm.nih.gov/9628870/ (accessed on 18 February 2023). [CrossRef]
122. Dechant, R.; Binda, M.; Lee, S.S.; Pelet, S.; Winderickx, J.; Peter, M. Cytosolic pH is a second messenger for glucose and regulates the PKA pathway through V-ATPase. *EMBO J.* **2010**, *29*, 2515–2526. Available online: http://emboj.embopress.org/cgi/doi/10.1038/emboj.2010.138 (accessed on 2 June 2020). [CrossRef]
123. Peeters, K.; Van Leemputte, F.; Fischer, B.; Bonini, B.M.; Quezada, H.; Tsytlonok, M.; Haesen, D.; Vanthienen, W.; Bernardes, N.; Gonzalez-Blas, C.B.; et al. Fructose-1,6-bisphosphate couples glycolytic flux to activation of Ras. *Nat. Commun.* **2017**, *8*, 922. Available online: https://pubmed.ncbi.nlm.nih.gov/29030545/ (accessed on 18 February 2023). [CrossRef]
124. Tanaka, K.; Lin, B.K.; Wood, D.R.; Tamanoi, F. IRA2, an upstream negative regulator of RAS in yeast, is a RAS GTPase-activating protein. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 468–472. Available online: http://www.ncbi.nlm.nih.gov/pubmed/1988946 (accessed on 1 April 2019). [CrossRef]
125. Tanaka, K.; Nakafuku, M.; Satoh, T.; Marshall, M.S.; Gibbs, J.B.; Matsumoto, K.; Kaziro, Y.; Toh-e, A.S. cerevisiae genes IRA1 and IRA2 encode proteins that may be functionally equivalent to mammalian ras GTPase activating protein. *Cell* **1990**, *60*, 803–807. Available online: https://www.sciencedirect.com/science/article/pii/009286749090094U?via%3Dihub (accessed on 13 March 2019). [CrossRef] [PubMed]
126. Tanaka, K.; Nakafuku, M.; Tamanoi, F.; Kaziro, Y.; Matsumoto, K.; Toh-e, A. IRA2, a second gene of *Saccharomyces cerevisiae* that encodes a protein with a domain homologous to mammalian ras GTPase-activating protein. *Mol. Cell Biol.* **1990**, *10*, 4303–4313. Available online: http://www.ncbi.nlm.nih.gov/pubmed/2164637 (accessed on 7 March 2019). [PubMed]
127. Tanaka, K.; Matsumoto, K.; Toh-E, A. IRA1, an inhibitory regulator of the RAS-cyclic AMP pathway in *Saccharomyces cerevisiae*. *Mol. Cell Biol.* **1989**, *9*, 757–768. Available online: http://www.ncbi.nlm.nih.gov/pubmed/2540426 (accessed on 1 April 2019). [PubMed]

128. Sass, P.; Field, J.; Nikawa, J.; Toda, T.; Wigler, M. Cloning and characterization of the high-affinity cAMP phosphodiesterase of *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 9303. [CrossRef]
129. Nikawa, J.; Sass, P.; Wigler, M. Cloning and characterization of the low-affinity cyclic AMP phosphodiesterase gene of *Saccharomyces cerevisiae*. *Mol. Cell Biol.* **1987**, *7*, 3629. [CrossRef] [PubMed]
130. Ma, P.; Wera, S.; Van Dijck, P.; Thevelein, J.M. The PDE1-encoded low-affinity phosphodiesterase in the yeast *Saccharomyces cerevisiae* has a specific function in controlling agonist-induced cAMP signaling. *Mol. Biol. Cell* **1999**, *10*, 91–104. Available online: https://pubmed.ncbi.nlm.nih.gov/9880329/ (accessed on 18 February 2023). [CrossRef]
131. Hu, Y.; Liu, E.; Bai, X.; Zhang, A. The localization and concentration of the *PDE2* -encoded high-affinity cAMP phosphodiesterase is regulated by cAMP-dependent protein kinase A in the yeast *Saccharomyces cerevisiae*. *FEMS Yeast Res.* **2010**, *10*, 177–187. Available online: https://academic.oup.com/femsyr/article-lookup/doi/10.1111/j.1567-1364.2009.00598.x (accessed on 26 May 2020). [CrossRef]
132. Griffioen, G.; Thevelein, J.M. Molecular mechanisms controlling the localisation of protein kinase A. In *Current Genetics*; Springer: Berlin/Heidelberg, Germany, 2002; Volume 41, pp. 199–207.
133. Griffioen, G.; Anghileri, P.; Imre, E.; Baroni, M.D.; Ruis, H. Nutritional control of nucleocytoplasmic localization of cAMP-dependent protein kinase catalytic and regulatory subunits in *Saccharomyces cerevisiae*. *J. Biol. Chem.* **2000**, *275*, 1449–1456. Available online: http://www.ncbi.nlm.nih.gov/pubmed/10625697 (accessed on 24 January 2019). [CrossRef]
134. Tudisca, V.; Recouvreux, V.; Moreno, S.; Boy-Marcotte, E.; Jacquet, M.; Portela, P. Differential localization to cytoplasm, nucleus or P-bodies of yeast PKA subunits under different growth conditions. *Eur. J. Cell Biol.* **2010**, *89*, 339–348. Available online: https://www.sciencedirect.com/science/article/pii/S017193350900301X?via%3Dihub (accessed on 11 February 2019). [CrossRef]
135. Colledge, M.; Scott, J.D. AKAPs: From structure to function. *Trends Cell Biol.* **1999**, *9*, 216–221. Available online: https://www.sciencedirect.com/science/article/pii/S0962892499015585?via%3Dihub (accessed on 7 March 2019). [CrossRef]
136. Dolinsky, W.; Paolillo, R.; D'apice, S.; Schiattarella, G.G.; Ameri, P.; Borzacchiello, D.; Catalucci, D.; Chimenti, C.; Crott, L.; Sciarretta, S.; et al. Mitochondrial a Kinase Anchor Proteins in Cardiovascular Health and Disease: A Review Article on Behalf of the Working Group on Cellular and Molecular Biology of the Heart of the Italian Society of Cardiology. *Int. J. Mol. Sci.* **2022**, *23*, 7691. Available online: https://www.mdpi.com/1422-0067/23/14/7691/htm (accessed on 5 September 2022).
137. Søberg, K.; Skålhegg, B.S. The Molecular Basis for Specificity at the Level of the Protein Kinase a Catalytic Subunit. *Front. Endocrinol* **2018**, *9*, 538. Available online: https://www.frontiersin.org/article/10.3389/fendo.2018.00538/full (accessed on 26 March 2019). [CrossRef]
138. Taskén, K.; Aandahl, E.M. Localized Effects of cAMP Mediated by Distinct Routes of Protein Kinase, A. *Physiol. Rev.* **2004**, *84*, 137–167. Available online: http://www.physiology.org/doi/10.1152/physrev.00021.2003 (accessed on 19 July 2019). [CrossRef]
139. Kocik, R.A.; Gasch, A.P. Breadth and Specificity in Pleiotropic Protein Kinase A Activity and Environmental Responses. *Front. Cell Dev. Biol.* **2022**, *10*, 334. [CrossRef]
140. Langeberg, L.K.; Scott, J.D. A-kinase-anchoring proteins. *J. Cell Sci.* **2005**, *118*, 3217–3220. Available online: https://journals.biologists.com/jcs/article/118/15/3217/28454/A-kinase-anchoring-proteins (accessed on 11 November 2022). [CrossRef]
141. Houslay, M.D. Underpinning compartmentalised cAMP signalling through targeted cAMP breakdown. *Trends Biochem. Sci.* **2010**, *35*, 91–100. Available online: https://www.sciencedirect.com/science/article/pii/S0968000409001923?via%3Dihub (accessed on 13 March 2019). [CrossRef]
142. Torres-Quesada, O.; Mayrhofer, J.E.; Stefan, E. The many faces of compartmentalized PKA signalosomes. *Cell Signal* **2017**, *37*, 1–11. Available online: https://www.sciencedirect.com/science/article/pii/S0898656817301420?via%3Dihub (accessed on 26 March 2019). [CrossRef] [PubMed]
143. Baillie, G.S.; Scott, J.D.; Houslay, M.D. Compartmentalisation of phosphodiesterases and protein kinase A: Opposites attract. *FEBS Lett.* **2005**, *579*, 3264–3270. Available online: http://doi.wiley.com/10.1016/j.febslet.2005.03.089 (accessed on 8 March 2019). [CrossRef] [PubMed]
144. Sample, V.; DiPilato, L.M.; Yang, J.H.; Ni, Q.; Saucerman, J.J.; Zhang, J. Regulation of nuclear PKA revealed by spatiotemporal manipulation of cyclic AMP. *Nat. Chem. Biol.* **2012**, *8*, 375–382. Available online: http://www.nature.com/articles/nchembio.799 (accessed on 13 March 2019). [CrossRef] [PubMed]
145. Hess, K.C.; Liu, J.; Manfredi, G.; Mühlschlegel, F.A.; Buck, J.; Levin, L.R.; Barrientos, A. A mitochondrial CO_2 -adenylyl cyclase-cAMP signalosome controls yeast normoxic cytochrome *c* oxidase activity. *FASEB J.* **2014**, *28*, 4369–4380. Available online: http://www.fasebj.org/doi/10.1096/fj.14-252890 (accessed on 9 April 2019). [CrossRef] [PubMed]
146. Galello, F.; Moreno, S.; Rossi, S. Interacting proteins of protein kinase A regulatory subunit in *Saccharomyces cerevisiae*. *J. Proteomics.* **2014**, *109*, 261–275. [CrossRef]
147. Filteau, M.; Diss, G.; Torres-Quiroz, F.; Dubé, A.K.; Schraffl, A.; Bachmann, V.A. Gagnon-Arsenault, I.; Chrétien, A.; Steunou, A.; Dionne, U.; et al. Systematic identification of signal integration by protein kinase, A. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 4501–4506. Available online: http://www.ncbi.nlm.nih.gov/pubmed/25831502 (accessed on 31 March 2019). [CrossRef] [PubMed]
148. Griffioen, G.; Branduardi, P.; Ballarini, A.; Anghileri, P.; Norbeck, J.; Baroni, M.D.; Ruis, H. Nucleocytoplasmic distribution of budding yeast protein kinase A regulatory subunit Bcy1 requires Zds1 and is regulated by Yak1-dependent phosphorylation of its targeting domain. *Mol. Cell Biol.* **2001**, *21*, 511–523. Available online: http://www.ncbi.nlm.nih.gov/pubmed/11134339 (accessed on 25 January 2019). [CrossRef]

149. Wagner, E.R.; Nightingale, N.M.; Jen, A.; Overmyer, K.A.; McGee, M.; Coon, J.J.; Gasch, A.P. PKA regulatory subunit Bcy1 couples growth, lipid metabolism, and fermentation during anaerobic xylose growth in *Saccharomyces cerevisiae*. *PLoS Genet* **2023**, *19*, e1010593. [CrossRef]
150. Ye, T.; Elbing, K.; Hohmann, S. The pathway by which the yeast protein kinase Snf1p controls acquisition of sodium tolerance is different from that mediating glucose regulation. *Microbiology* **2008**, *154*, 2814–2826. Available online: https://www.microbiologyresearch.org/content/journal/micro/10.1099/mic.0.2008/020149-0 (accessed on 13 June 2023). [CrossRef]
151. Shashkova, S.; Welkenhuysen, N.; Hohmann, S. Molecular communication: Crosstalk between the Snf1 and other signaling pathways. *FEMS Yeast Res.* **2015**, *15*, 26. [CrossRef] [PubMed]
152. Ashrafi, K.; Lin, S.S.; Manchester, J.K.; Gordon, J.I. Sip2p and its partner Snf1p kinase affect aging in, S. *cerevisiae. Genes. Dev.* **2000**, *14*, 1872–1885. Available online: http://genesdev.cshlp.org/content/14/15/1872.full (accessed on 25 January 2023). [CrossRef] [PubMed]
153. Lin, S.S.; Manchester, J.K.; Gordon, J.I. Sip2, an N-myristoylated β subunit of Snf1 kinase, regulates aging in *Saccharomyces cerevisiae* by affecting cellular histone kinase activity, recombination at rDNA loci, and silencing. *J. Biol. Chem.* **2003**, *278*, 13390–13397. [CrossRef]
154. Hedbacker, K.; Carlson, M. SNF1/AMPK pathways in yeast. *Front. Biosci.* **2008**, *13*, 2408–2420. Available online: https://pubmed.ncbi.nlm.nih.gov/17981722/ (accessed on 25 January 2023). [CrossRef]
155. Usaite, R.; Jewett, M.C.; Oliveira, A.P.; Yates, J.R.; Olsson, L.; Nielsen, J. Reconstruction of the yeast Snf1 kinase regulatory network reveals its role as a global energy regulator. *Mol. Syst. Biol.* **2009**, *5*, 319. Available online: https://pubmed.ncbi.nlm.nih.gov/19888214/ (accessed on 25 January 2023). [CrossRef]
156. Simpson-Lavy, K.J.; Kupiec, M. The polyHIS Tract of Yeast AMPK Coordinates Carbon Metabolism with Iron Availability. *Int. J. Mol. Sci.* **2023**, *24*, 1368. Available online: https://www.mdpi.com/1422-0067/24/2/1368/htm (accessed on 30 January 2023). [CrossRef] [PubMed]
157. Kuchin, S.; Treich, I.; Carlson, M. A regulatory shortcut between the Snf1 protein 7 kinase and RNA polymerase II holoenzyme. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 7916–7920. Available online: https://www.pnas.org/doi/abs/10.1073/pnas.140109897 (accessed on 19 January 2023). [CrossRef] [PubMed]
158. Young, E.T.; Zhang, C.; Shokat, K.M.; Parua, P.K.; Braun, K.A. The AMP-activated protein kinase Snf1 regulates transcription factor binding, RNA polymerase II activity, and mRNA stability of glucose-repressed genes in *Saccharomyces cerevisiae*. *J. Biol. Chem.* **2012**, *287*, 29021–29034. Available online: http://www.jbc.org/article/S0021925820684332/fulltext (accessed on 19 January 2023). [CrossRef]
159. Jiang, R.; Carlson, M. The Snf1 protein kinase and its activating subunit, Snf4, interact with distinct domains of the Sip1/Sip2/Gal83 component in the kinase complex. *Mol. Cell Biol.* **1997**, *17*, 2099–2106. Available online: https://journals.asm.org/doi/10.1128/MC.B.17.4.2099 (accessed on 25 January 2023). [CrossRef] [PubMed]
160. Celenza, J.L.; Eng, F.J.; Carlson, M. Molecular analysis of the SNF4 gene of *Saccharomyces cerevisiae*: Evidence for physical association of the SNF4 protein with the SNF1 protein kinase. *Mol. Cell Biol.* **1989**, *9*, 5045–5054. Available online: https://pubmed.ncbi.nlm.nih.gov/2481228/ (accessed on 25 January 2023).
161. Leech, A.; Nath, N.; McCartney, R.R.; Schmidt, M.C. Isolation of mutations in the catalytic domain of the snf1 kinase that render its activity independent of the snf4 subunit. *Eukaryot. Cell* **2003**, *2*, 265–273. Available online: https://pubmed.ncbi.nlm.nih.gov/12684376/ (accessed on 25 January 2023). [CrossRef] [PubMed]
162. Momcilovic, M.; Iram, S.H.; Liu, Y.; Carlson, M. Roles of the glycogen-binding domain and Snf4 in glucose inhibition of SNF1 protein kinase. *J. Biol. Chem.* **2008**, *283*, 19521–19529. Available online: https://pubmed.ncbi.nlm.nih.gov/18474591/ (accessed on 25 January 2023). [CrossRef] [PubMed]
163. Mayer, F.V.; Heath, R.; Underwood, E.; Sanders, M.J.; Carmena, D.; McCartney, R.R.; Leiper, F.C.; Xiao, B.; Jing, C.; Walker, P.A.; et al. ADP regulates SNF1, the *Saccharomyces cerevisiae* homolog of AMP-activated protein kinase. *Cell Metab.* **2011**, *14*, 707–714. Available online: https://pubmed.ncbi.nlm.nih.gov/22019086/ (accessed on 25 January 2023). [CrossRef]
164. MC, S.; RR, M. beta-subunits of Snf1 kinase are required for kinase function and substrate definition. *EMBO J.* **2000**, *19*, 4936–4943. Available online: https://pubmed.ncbi.nlm.nih.gov/10990457/ (accessed on 25 January 2023).
165. Simpson-Lavy, K.J.; Kupiec, M. Regulation of yeast Snf1 (AMPK) by a polyhistidine containing pH sensing module. *iScience.* **2022**, *25*, 105083. [CrossRef]
166. Wilson, W.A.; Hawley, S.A.; Hardie, D.G. Glucose repression/derepression in budding yeast: SNF1 protein kinase is activated by phosphorylation under derepressing conditions, and this correlates with a high AMP:ATP ratio. *Curr. Biol.* **1996**, *6*, 1426–1434. Available online: https://pubmed.ncbi.nlm.nih.gov/8939604/ (accessed on 25 January 2023). [CrossRef]
167. Simpson-Lavy, K.; Xu, T.; Johnston, M.; Kupiec, M. The Std1 Activator of the Snf1/AMPK Kinase Controls Glucose Response in Yeast by a Regulated Protein Aggregation. *Mol. Cell.* **2017**, *68*, 1120–1133.e3. [CrossRef]
168. Zhang, M.; Galdieri, L.; Vancura, A. The yeast AMPK homolog SNF1 regulates acetyl coenzyme A homeostasis and histone acetylation. *Mol. Cell Biol.* **2013**, *33*, 4701–4717. Available online: https://pubmed.ncbi.nlm.nih.gov/24081331/ (accessed on 25 January 2023). [CrossRef] [PubMed]
169. Sanz, P. Snf1 protein kinase: A key player in the response to cellular stress in yeast. *Biochem. Soc. Trans.* **2003**, *31 Pt 1*, 178–181. Available online: https://pubmed.ncbi.nlm.nih.gov/12546680/ (accessed on 25 January 2023). [CrossRef] [PubMed]

170. Hahn, J.S.; Thiele, D.J. Activation of the *Saccharomyces cerevisiae* heat shock transcription factor under glucose starvation conditions by Snf1 protein kinase. *J. Biol. Chem.* **2004**, *279*, 5169–5176. Available online: https://pubmed.ncbi.nlm.nih.gov/14612437/ (accessed on 25 January 2023). [CrossRef]
171. Mizuno, T.; Masuda, Y.; Irie, K. The *Saccharomyces cerevisiae* AMP.K.; Snf1, Negatively Regulates the Hog1 MAPK Pathway in ER Stress Response. *PLoS Genet.* **2015**, *11*, e1005491. Available online: https://pubmed.ncbi.nlm.nih.gov/26394309/ (accessed on 25 January 2023). [CrossRef]
172. Back, S.H.; Schröder, M.; Lee, K.; Zhang, K.; Kaufman, R.J. ER stress signaling by regulated splicing: IRE1/HAC1/XBP1. *Methods* **2005**, *35*, 395–416. Available online: https://pubmed.ncbi.nlm.nih.gov/15804613/ (accessed on 25 January 2023). [CrossRef] [PubMed]
173. Portillo, F.; Mulet, J.M.; Serrano, R. A role for the non-phosphorylated form of yeast Snf1: Tolerance to toxic cations and activation of potassium transport. *FEBS Lett.* **2005**, *579*, 512–516. Available online: https://pubmed.ncbi.nlm.nih.gov/15642368/ (accessed on 25 January 2023). [CrossRef]
174. Dubacq, C.; Chevalier, A.; Mann, C. The protein kinase Snf1 is required for tolerance to the ribonucleotide reductase inhibitor hydroxyurea. *Mol. Cell Biol.* **2004**, *24*, 2560–2572. Available online: https://pubmed.ncbi.nlm.nih.gov/14993292/ (accessed on 25 January 2023). [CrossRef]
175. Pérez-Sampietro, M.; Casas, C.; Herrero, E. The AMPK Family Member Snf1 Protects *Saccharomyces cerevisiae* Cells upon Glutathione Oxidation. *PLoS ONE* **2013**, *8*, e58283. [CrossRef]
176. Hong, S.P.; Carlson, M. Regulation of snf1 protein kinase in response to environmental stress. *J. Biol. Chem.* **2007**, *282*, 16838–16845. Available online: https://pubmed.ncbi.nlm.nih.gov/17438333/ (accessed on 25 January 2023). [CrossRef] [PubMed]
177. Platara, M.; Ruiz, A.; Serrano, R.; Palomino, A.; Moreno, F.; Ariño, J. The transcriptional response of the yeast Na(+)-ATPase ENA1 gene to alkaline stress involves three main signaling pathways. *J. Biol. Chem.* **2006**, *281*, 36632–36642. Available online: https://pubmed.ncbi.nlm.nih.gov/17023428/ (accessed on 25 January 2023). [CrossRef]
178. Mori, K. Signalling pathways in the unfolded protein response: Development from yeast to mammals. *J. Biochem.* **2009**, *146*, 743–750. Available online: https://pubmed.ncbi.nlm.nih.gov/19861400/ (accessed on 25 January 2023). [CrossRef]
179. Walter, P.; Ron, D. The unfolded protein response: From stress pathway to homeostatic regulation. *Science* **2011**, *334*, 1081–1086. Available online: https://pubmed.ncbi.nlm.nih.gov/22116877/ (accessed on 25 January 2023). [CrossRef] [PubMed]
180. Ferrer-Dalmau, J.; Randez-Gil, F.; Marquina, M.; Prieto, J.A.; Casamayor, A. Protein kinase Snf1 is involved in the proper regulation of the unfolded protein response in *Saccharomyces cerevisiae*. *Biochem. J.* **2015**, *468*, 33–47. Available online: https://pubmed.ncbi.nlm.nih.gov/25730376/ (accessed on 25 January 2023). [CrossRef]
181. Lu, J.Y.; Lin, Y.Y.; Sheu, J.C.; Wu, J.T.; Lee, F.J.; Chen, Y.; Lin, M.; Chiang, F.T.; Tai, T.; Berger, S.L.; et al. Acetylation of yeast AMPK controls intrinsic aging independently of caloric restriction. *Cell* **2011**, *146*, 969–979. Available online: https://pubmed.ncbi.nlm.nih.gov/21906795/ (accessed on 25 January 2023). [CrossRef] [PubMed]
182. Wierman, M.B.; Maqani, N.; Strickler, E.; Li, M.; Smith, J.S. Caloric Restriction Extends Yeast Chronological Life Span by Optimizing the Snf1 (AMPK) Signaling Pathway. *Mol. Cell Biol.* **2017**, *37*, e00562-16. Available online: https://pubmed.ncbi.nlm.nih.gov/28373292/ (accessed on 25 January 2023). [CrossRef]
183. Maqani, N.; Fine, R.D.; Shahid, M.; Li, M.; Enriquez-Hesles, E.; Smith, J.S. Spontaneous mutations in CYC8 and MIG1 suppress the short chronological lifespan of budding yeast lacking SNF1/AMPK. *Microb. Cell* **2018**, *5*, 233–248. Available online: https://pubmed.ncbi.nlm.nih.gov/29796388/ (accessed on 25 January 2023). [CrossRef]
184. Hedbacker, K.; Townley, R.; Carlson, M. Cyclic AMP-Dependent Protein Kinase Regulates the Subcellular Localization of Snf1-Sip1 Protein Kinase. *Mol. Cell Biol.* **2004**, *24*, 1836–1843. [CrossRef]
185. Barrett, L.; Orlova, M.; Maziarz, M.; Kuchin, S. Protein kinase A contributes to the negative control of Snf1 protein kinase in *Saccharomyces cerevisiae*. *Eukaryot. Cell* **2012**, *11*, 119–128. Available online: https://pubmed.ncbi.nlm.nih.gov/22140226/ (accessed on 25 January 2023). [CrossRef]
186. Nicastro, R.; Tripodi, F.; Gaggini, M.; Castoldi, A.; Reghellin, V.; Nonnis, S.; Tedeschi, G.; Coccetti, P. Snf1 phosphorylates adenylate cyclase and negatively regulates protein kinase A-dependent transcription in *Saccharomyces cerevisiae*. *J. Biol. Chem.* **2015**, *290*, 24715–24726. [CrossRef]
187. Maeda, T.; Wurgler-Murphy, S.M.; Saito, H. A two-component system that regulates an osmosensing MAP kinase cascade in yeast. *Nature* **1994**, *369*, 242–245. Available online: https://pubmed.ncbi.nlm.nih.gov/8183345/ (accessed on 19 February 2023). [CrossRef] [PubMed]
188. Maeda, T.; Takekawa, M.; Saito, H. Activation of Yeast PBS2 MAPKK by MAPKKKs or by Binding of an SH3-Containing Omosensor. *Science* **1995**, *269*, 554–558. Available online: https://www.science.org/doi/10.1126/science.7624781 (accessed on 10 February 2023). [CrossRef] [PubMed]
189. Ota, I.M.; Varshavsky, A. A yeast protein similar to bacterial two-component regulators. *Science* **1993**, *262*, 566–569. Available online: https://pubmed.ncbi.nlm.nih.gov/8211183/ (accessed on 1 June 2023). [CrossRef]
190. Brewster, J.L.; De Valoir, T.; Dwyer, N.D.; Winter, E.; Gustin, M.C. An osmosensing signal transduction pathway in yeast. *Science* **1993**, *259*, 1760–1763. Available online: https://pubmed.ncbi.nlm.nih.gov/7681220/ (accessed on 19 February 2023). [CrossRef] [PubMed]
191. Tatebayashi, K.; Takekawa, M.; Saito, H. A docking site determining specificity of Pbs2 MAPKK for Ssk2/Ssk22 MAPKKKs in the yeast HOG pathway. *EMBO J.* **2003**, *22*, 3624. [CrossRef] [PubMed]

192. Boguslawski, G. PBS2, a yeast gene encoding a putative protein kinase, interacts with the RAS2 pathway and affects osmotic sensitivity of *Saccharomyces cerevisiae*. *J. Gen. Microbiol.* **1992**, *138*, 2425–2432. Available online: https://pubmed.ncbi.nlm.nih.gov/1479360/ (accessed on 1 June 2023). [CrossRef]
193. Posas, F.; Saito, H. Osmotic activation of the HOG MAPK pathway via Ste11p MAPKKK: Scaffold role of Pbs2p MAPKK. *Science* **1997**, *276*, 1702–1708. Available online: https://pubmed.ncbi.nlm.nih.gov/9180081/ (accessed on 19 February 2023). [CrossRef]
194. De Nadal, E.; Posas, F. The HOG pathway and the regulation of osmoadaptive responses in yeast. *FEMS Yeast Res.* **2022**, *22*, 1. Available online: https://academic.oup.com/femsyr/article/22/1/foac013/6543702 (accessed on 20 January 2023). [CrossRef]
195. Albertyn, J.; Hohmann, S.; Thevelein, J.M.; Prior, B.A. GPD1, which encodes glycerol-3-phosphate dehydrogenase, is essential for growth under osmotic stress in *Saccharomyces cerevisiae*, and its expression is regulated by the high-osmolarity glycerol response pathway. *Mol. Cell Biol.* **1994**, *14*, 4135–4144. Available online: http://www.ncbi.nlm.nih.gov/pubmed/8196651 (accessed on 24 January 2019).
196. Klipp, E.; Nordlander, B.; Krüger, R.; Gennemark, P.; Hohmann, S. Integrative model of the response of yeast to osmotic shock. *Nat. Biotechnol.* **2005**, *23*, 975–982. Available online: https://pubmed.ncbi.nlm.nih.gov/16025103/ (accessed on 10 February 2023). [CrossRef]
197. Muzzey, D.; Gómez-Uribe, C.A.; Mettetal, J.T.; van Oudenaarden, A. A systems-level analysis of perfect adaptation in yeast osmoregulation. *Cell* **2009**, *138*, 160–171. Available online: https://pubmed.ncbi.nlm.nih.gov/19596242/ (accessed on 1 June 2023). [CrossRef] [PubMed]
198. Hao, N.; Behar, M.; Parnell, S.C.; Torres, M.P.; Borchers, C.H.; Elston, T.C.C.; Dohlman, H.G. A systems-biology analysis of feedback inhibition in the Sho1 osmotic-stress-response pathway. *Curr. Biol.* **2007**, *17*, 659–667. Available online: https://pubmed.ncbi.nlm.nih.gov/17363249/ (accessed on 10 February 2023). [CrossRef] [PubMed]
199. Hao, N.; Zeng, Y.; Elston, T.C.; Dohlman, H.G. Control of MAPK specificity by feedback phosphorylation of shared adaptor protein Ste50. *J. Biol. Chem.* **2008**, *283*, 33798–33802. Available online: https://pubmed.ncbi.nlm.nih.gov/18854322/ (accessed on 1 June 2023). [CrossRef] [PubMed]
200. Yamamoto, K.; Tatebayashi, K.; Tanaka, K.; Saito, H. Dynamic control of yeast MAP kinase network by induced association and dissociation between the Ste50 scaffold and the Opy2 membrane anchor. *Mol. Cell* **2010**, *40*, 87–98. Available online: https://pubmed.ncbi.nlm.nih.gov/20932477/ (accessed on 1 June 2023). [CrossRef] [PubMed]
201. Molin, C.; Jauhiainen, A.; Warringer, J.; Nerman, O.; Sunnerhagen, P.E.R. mRNA stability changes precede changes in steady-state mRNA amounts during hyperosmotic stress. *RNA* **2009**, *15*, 600. Available online: http://www.rnajournal.org/cgi/doi/10.1261/rna.1403509 (accessed on 10 February 2023). [CrossRef]
202. Romero-Santacreu, L.; Moreno, J.; Pérez-Ortín, J.E.; Alepuz, P. Specific and global regulation of mRNA stability during osmotic stress in *Saccharomyces cerevisiae*. *RNA* **2009**, *15*, 1110–1120. Available online: https://pubmed.ncbi.nlm.nih.gov/19369426/ (accessed on 10 February 2023). [CrossRef]
203. Miller, C.; Schwalb, B.; Maier, K.; Schulz, D.; Dümcke, S.; Zacher, B.; Mayer, A.; Sydow, J.; Marcinowski, L. Dölken, L.; et al. Dynamic transcriptome analysis measures rates of mRNA synthesis and decay in yeast. *Mol. Syst. Biol.* **2011**, *7*, 458. Available online: https://pubmed.ncbi.nlm.nih.gov/21206491/ (accessed on 10 February 2023). [CrossRef]
204. Alepuz, P.M.; De Nadal, E.; Zapater, M.; Ammerer, G.; Posas, F. Osmostress-induced transcription by Hot1 depends on a Hog1-mediated recruitment of the RNA Pol II. *EMBO J.* **2003**, *22*, 2433. [CrossRef]
205. Proft, M.; Struhl, K. Hog1 kinase converts the Sko1-Cyc8-Tup1 repressor complex into an activator that recruits SAGA and SWI/SNF in response to osmotic stress. *Mol. Cell* **2002**, *9*, 1307–1317. Available online: https://pubmed.ncbi.nlm.nih.gov/12086627/ (accessed on 1 June 2023). [CrossRef]
206. Proft, M.; Struhl, K. MAP kinase-mediated stress relief that precedes and regulates the timing of transcriptional induction. *Cell* **2004**, *118*, 351–361. Available online: https://pubmed.ncbi.nlm.nih.gov/15294160/ (accessed on 1 June 2023). [CrossRef] [PubMed]
207. Proft, M.; Mas, G.; de Nadal, E.; Vendrell, A.; Noriega, N.; Struhl, K.; Posas, F. The stress-activated Hog1 kinase is a selective transcriptional elongation factor for genes responding to osmotic stress. *Mol. Cell* **2006**, *23*, 241–250. Available online: https://pubmed.ncbi.nlm.nih.gov/16857590/ (accessed on 1 June 2023). [CrossRef] [PubMed]
208. Dihazi, H.; Kessler, R.; Eschrich, K. High osmolarity glycerol (HOG) pathway-induced phosphorylation and activation of 6-phosphofructo-2-kinase are essential for glycerol accumulation and yeast cell proliferation under hyperosmotic stress. *J. Biol. Chem.* **2004**, *279*, 23961–23968. Available online: http://www.ncbi.nlm.nih.gov/pubmed/15037628 (accessed on 24 January 2019). [CrossRef] [PubMed]
209. Mollapour, M.; Piper, P.W. Hog1 mitogen-activated protein kinase phosphorylation targets the yeast Fps1 aquaglyceroporin for endocytosis, thereby rendering cells resistant to acetic acid. *Mol. Cell Biol.* **2007**, *27*, 6446–6456. Available online: https://pubmed.ncbi.nlm.nih.gov/17620418/ (accessed on 25 January 2023). [CrossRef]
210. Westfall, P.J.; Patterson, J.C.; Chen, R.E.; Thorner, J. Stress resistance and signal fidelity independent of nuclear MAPK function. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 12212–12217. Available online: https://pubmed.ncbi.nlm.nih.gov/18719124/ (accessed on 10 February 2023). [CrossRef]
211. Beese, S.E.; Negishi, T.; Levin, D.E. Identification of positive regulators of the yeast fps1 glycerol channel. *PLoS Genet.* **2009**, *5*, 11. Available online: https://pubmed.ncbi.nlm.nih.gov/19956799/ (accessed on 10 February 2023). [CrossRef]

212. Bouwman, J.; Kiewiet, J.; Lindenbergh, A.; Van Eunen, K.; Siderius, M.; Bakker, B.M. Metabolic regulation rather than de novo enzyme synthesis dominates the osmo-adaptation of yeast. *Yeast* **2011**, *28*, 43–53. Available online: https://pubmed.ncbi.nlm.nih.gov/20803479/ (accessed on 10 February 2023). [CrossRef]
213. Hernández-Elvira, M.; Martínez-Gómez, R.; Domínguez-Martin, E.; Méndez, A.; Kawasaki, L.; Ongay-Larios, L.; Coria, R. Tunicamycin Sensitivity-Suppression by High Gene Dosage Reveals New Functions of the Yeast Hog1 MAP Kinase. *Cells* **2019**, *8*, 710. Available online: https://pubmed.ncbi.nlm.nih.gov/31336877/ (accessed on 31 May 2023). [CrossRef]
214. Wagner, E.R.; Myers, K.S.; Riley, N.M.; Coon, J.J.; Gasch, A.P. PKA and HOG signaling contribute separable roles to anaerobic xylose fermentation in yeast engineered for biofuel production. *PLoS ONE* **2019**, *14*, e0212389. Available online: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0212389 (accessed on 15 December 2022). [CrossRef]
215. Klein, C.; Struhl, K. Protein Kinase A Mediates Growth-Regulated Expression of Yeast Ribosomal Protein Genes by Modulating RAP1 Transcriptional Activity. *Mol. Cell. Biol.* **1994**, *14*, 1920–1928. [CrossRef] [PubMed]
216. de la Cruz, J.; Gómez-Herreros, F.; Rodríguez-Galán, O.; Begley, V.; de la Cruz Muñoz-Centeno, M.; Chávez, S. Feedback regulation of ribosome assembly. *Curr. Genet.* **2018**, *64*, 393–404. Available online: https://pubmed.ncbi.nlm.nih.gov/29022131/ (accessed on 1 June 2023). [CrossRef]
217. Jorgensen, P.; Rupeš, I.; Sharom, J.R.; Schneper, L.; Broach, J.R.; Tyers, M. A dynamic transcriptional network communicates growth potential to ribosome synthesis and critical cell size. *Genes. Dev.* **2004**, *18*, 2491–2505. Available online: http://genesdev.cshlp.org/content/18/20/2491.full (accessed on 25 June 2020). [CrossRef] [PubMed]
218. Neuman-Silberberg, F.S.; Bhattacharya, S.; Broach, J.R. Nutrient availability and the RAS/cyclic AMP pathway both induce expression of ribosomal protein genes in *Saccharomyces cerevisiae* but by different mechanisms. *Mol. Cell Biol.* **1995**, *15*, 3187–3196. Available online: http://www.ncbi.nlm.nih.gov/pubmed/7760815 (accessed on 24 January 2019). [CrossRef] [PubMed]
219. Zurita-Martinez, S.A.; Cardenas, M.E. Tor and cyclic AMP-protein kinase A: Two parallel pathways regulating expression of genes required for cell growth. *Eukaryot. Cell* **2005**, *4*, 63–71. Available online: https://pubmed.ncbi.nlm.nih.gov/15643061/ (accessed on 10 February 2023). [CrossRef] [PubMed]
220. Jorgensen, P.; Nishikawa, J.L.; Breitkreutz, B.J.; Tyers, M. Systematic identification of pathways that couple cell growth and division in yeast. *Science* **2002**, *297*, 395–400. Available online: https://science.sciencemag.org/content/297/5580/395 (accessed on 2 July 2020). [CrossRef] [PubMed]
221. Wang, Y.; Pierce, M.; Schneper, L.; Güldal, C.G.; Zhang, X.; Tavazoie, S.; Broach, J.R. Ras and Gpa2 mediate one branch of a redundant glucose signaling pathway in yeast. *PLoS Biol.* **2004**, *2*, 610–622. Available online: https://pubmed.ncbi.nlm.nih.gov/15138498/ (accessed on 10 February 2023). [CrossRef]
222. Fingerman, I.; Nagaraj, V.; Norris, D.; Vershon, A.K. Sfp1 plays a key role in yeast ribosome biogenesis. *Eukaryot. Cell* **2003**, *2*, 1061–1068. Available online: https://pubmed.ncbi.nlm.nih.gov/14555489/ (accessed on 10 February 2023). [CrossRef]
223. Marion, R.M.; Regev, A.; Segal, E.; Barash, Y.; Koller, D.; Friedman, N.; O'Shea, E.K. Sfp1 is a stress- and nutrient-sensitive regulator of ribosomal protein gene expression. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 14315–14322. Available online: https://pubmed.ncbi.nlm.nih.gov/15353587/ (accessed on 10 February 2023). [CrossRef]
224. Pessina, S.; Tsiarentsyeva, V.; Busnelli, S.; Vanoni, M.; Alberghina, L.; Coccetti, P. Snf1/AMPK promotes S-phase entrance by controlling CLB5 transcription in budding yeast. *Cell Cycle* **2010**, *9*, 2189–2200. Available online: https://pubmed.ncbi.nlm.nih.gov/20505334/ (accessed on 10 February 2023). [CrossRef]
225. Koch, C.; Moll, T.; Neuberg, M.; Ahorn, H.; Nasmyth, K. A role for the transcription factors Mbp1 and Swi4 in progression from G1 to S phase. *Science* **1993**, *261*, 1551–1557. Available online: https://pubmed.ncbi.nlm.nih.gov/8372350/ (accessed on 10 February 2023). [CrossRef]
226. Busnelli, S.; Tripodi, F.; Nicastro, R.; Cirulli, C.; Tedeschi, G.; Pagliarin, R.; Alberghina, L.; Coccetti, P. Snf1/AMPK promotes SBF and MBF-dependent transcription in budding yeast. *Biochim. Biophys. Acta* **2013**, *1833*, 3254–3264. Available online: https://pubmed.ncbi.nlm.nih.gov/24084603/ (accessed on 10 February 2023). [CrossRef] [PubMed]
227. Tripodi, F.; Fraschini, R.; Zocchi, M.; Reghellin, V.; Coccetti, P. Snf1/AMPK is involved in the mitotic spindle alignment in *Saccharomyces cerevisiae*. *Sci. Rep.* **2018**, *8*, 5853. Available online: http://www.nature.com/articles/s41598-018-24252-y (accessed on 3 June 2019). [CrossRef]
228. Moore, J.K.; Cooper, J.A. Coordinating mitosis with cell polarity: Molecular motors at the cell cortex. *Semin. Cell Dev. Biol.* **2010**, *21*, 283–289. Available online: https://pubmed.ncbi.nlm.nih.gov/20109571/ (accessed on 10 February 2023). [CrossRef]
229. Vendrell, A.; Martánez-Pastor, M.; González-Novo, A.; Pascual-Ahuir, A.; Sinclair, D.A.; Proft, M.; Posas, F. Sir2 histone deacetylase prevents programmed cell death caused by sustained activation of the Hog1 stress-activated protein kinase. *EMBO Rep.* **2011**, *12*, 1062. [CrossRef] [PubMed]
230. Maeda, T.; Tsai, A.Y.; Saito, H. Mutations in a protein tyrosine phosphatase gene (PTP2) and a protein serine/threonine phosphatase gene (PTC1) cause a synthetic growth defect in *Saccharomyces cerevisiae*. *Mol. Cell Biol.* **1993**, *13*, 5408–5417. Available online: https://pubmed.ncbi.nlm.nih.gov/8395005/ (accessed on 19 February 2023).
231. Escoté, X.; Zapater, M.; Clotet, J.; Posas, F. Hog1 mediates cell-cycle arrest in G1 phase by the dual targeting of Sic1. *Nat. Cell Biol.* **2004**, *6*, 997–1002. Available online: https://pubmed.ncbi.nlm.nih.gov/15448699/ (accessed on 19 February 2023). [CrossRef]

232. Adrover, M.À.; Zi, Z.; Duch, A.; Schaber, J.; González-Novo, A.; Jimenez, J.; Nadal-Ribelles, M.; Clotet, J.; Klipp, E.; Posas, F. Time-dependent quantitative multicomponent control of the G_1-S network by the stress-activated protein kinase Hog1 upon osmostress. *Sci. Signal* **2011**, *4*, 192. Available online: https://pubmed.ncbi.nlm.nih.gov/21954289/ (accessed on 19 February 2023). [CrossRef] [PubMed]
233. González-Novo, A.; Jiménez, J.; Clotet, J.; Nadal-Ribelles, M.; Cavero, S.; de Nadal, E.; Posas, F. Hog1 Targets Whi5 and Msa1 Transcription Factors To Downregulate Cyclin Expression upon Stress. *Mol. Cell Biol.* **2015**, *35*, 1606. [CrossRef]
234. Yaakov, G.; Duch, A.; García-Rubio, M.; Clotet, J.; Jimenez, J.; Aguilera, A.; Posas, F. The stress-activated protein kinase Hog1 mediates S phase delay in response to osmostress. *Mol. Biol. Cell* **2009**, *20*, 3572–3582. Available online: https://pubmed.ncbi.nlm.nih.gov/19477922/ (accessed on 19 February 2023). [CrossRef]
235. Duch, A.; Canal, B.; Barroso, S.I.; García-Rubio, M.; Seisenbacher, G.; Aguilera, A.; de Nadal, E.; Posas, F. Multiple signaling kinases target Mrc1 to prevent genomic instability triggered by transcription-replication conflicts. *Nat. Commun.* **2018**, *9*, 379. Available online: https://www.nature.com/articles/s41467-017-02756-x (accessed on 19 February 2023). [CrossRef]
236. Duch, A.; Felipe-Abrio, I.; Barroso, S.; Yaakov, G.; García-Rubio, M.; Aguilera, A.; de Nadal, E.; Posas, F. Coordinated control of replication and transcription by a SAPK protects genomic integrity. *Nature* **2013**, *493*, 116–121. Available online: https://pubmed.ncbi.nlm.nih.gov/23178807/ (accessed on 19 February 2023). [CrossRef]
237. Alexander, M.R.; Tyers, M.; Perret, M.; Craig, B.M.; Fang, K.S.; Gustin, M.C. Regulation of Cell Cycle Progression by Swe1p and Hog1p Following Hypertonic Stress. *Mol. Biol. Cell* **2001**, *12*, 53. [CrossRef] [PubMed]
238. Clotet, J.; Escoté, X.; Adrover, M.Á.; Yaakov, G.; Garí, E.; Aldea, M.; de Nadal, E.; Posas, F. Phosphorylation of Hsl1 by Hog1 leads to a G2 arrest essential for cell survival at high osmolarity. *EMBO J.* **2006**, *25*, 2338. [CrossRef]
239. Jiménez, J.; Queralt, E.; Posas, F.; de Nadal, E. The regulation of Net1/Cdc14 by the Hog1 MAPK upon osmostress unravels a new mechanism regulating mitosis. *Cell Cycle* **2020**, *19*, 2105. [CrossRef]
240. Tognetti, S.; Jiménez, J.; Viganò, M.; Duch, A.; Queralt, E.; de Nadal, E.; Posas, F. Hog1 activation delays mitotic exit via phosphorylation of Net1. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 8924–8933. Available online: https://pubmed.ncbi.nlm.nih.gov/32265285/ (accessed on 19 February 2023). [CrossRef]