Table S4: Functions of genes in the candidate region in BTA14.

XKR4 (XK Related 4) encodes a protein that has been suggested to promote exposure of phosphatidylserine by apoptotic cells [1]. Many peripheral and integral membrane proteins have phosphatidylserine-binding domains on their cytoplasmic surfaces which either provide a membrane anchor or affect activity. These domains can also determine trafficking within the cell. As an example, exophilin4/Slp2-a localizes on phosphatidylserine-enriched plasma membrane, and its N-terminal Rab27-binding domain (RBD27) specifically recognizes Rab27 on the surfaces of melanosomes and secretory granules prior to docking and fusion, with Rab27 dysfunction causing the Griscelli syndrome [2], a rare, autosomal recessive disorder, characterized by pigmentary dilution of the skin and the hair, the presence of large clumps of pigment in hair shafts and an accumulation of melanosomes in melanocytes. Interestingly, XKR4 was found in a candidate region for differential selection by contrasting three Korean cattle breeds displaying **different coat color phenotypes** [3] and detected within a selection signature in cattle with various **indicine introgression** levels [4]. Moreover, Sun et al. [5] demonstrate that another member of the XKR family, XKR5, is a novel negative regulator of **KIT signaling**.

TRNAT-AGU (Transfer RNA threonine) tRNA

TMEM68 (Transmembrane Protein 68) encodes a protein that has been suggested to belong to the glycerophospholipid acyltransferase family. Chang et al. [6] described it as an integral ER membrane protein and a putative acyltransferase involved in brain glycerolipid metabolism. Alike XKR4 (see above), TMEM68 was found in a candidate region for differential selection by contrasting three Korean cattle breeds displaying **different coat color phenotypes** [8]. In addition, it was found associated with various phenotypic traits in **cattle of indicine origin** [7,8].

TGS1 (Trimethylguanosine Synthase 1) encodes an essential cytoplasmic methyltransferase. Methyltransferases are involved in many different cellular processes including the post-transcriptional modification of RNAs. TGS1 catalyzes the 2 serial methylation steps for the conversion of the 7-monomethylguanosine (m7G) caps of snRNAs (small nuclear RNAs), including spliceosomal uridyl-rich small nuclear RNAs (UsnRNAs), and snoRNAs (small nucleolar RNAs) to a 2,2,7-trimethylguanosine (m(2,2,7)G) cap structure. The enzyme is specific for guanine, and N7 methylation must precede N2 methylation. Hypermethylation of the m7G cap of U snRNAs leads to their concentration in nuclear foci, their colocalization with coilin and the formation of canonical Cajal bodies (CBs). It plays a role in transcriptional regulation.

UsnRNA 5′-cap hypermethylation plays an important role during the biogenesis of UsnRNPs (uridyl-rich small nuclear ribonucleoprotein particles). In higher eukaryotes, the maturation of UsnRNPs comprises a nucleo-cytoplasmic transport cycle. Newly transcribed snRNAs U1, U2, U4 and U5 are exported to the cytoplasm in an m7 G cap-dependent manner, where assembly with seven Sm proteins occurs. This assembly process is mediated by the survival of motor neuron complex (SMN complex), a large multiprotein complex. The m7 G cap is subsequently hypermethylated by TGS1 and the resulting m3G cap is recognized by the nuclear import adaptor snurportin1, which binds to the general nuclear import receptor importin. Hence, the m3G cap serves as nuclear import signal that indicates the completed assembly of

the core UsnRNP particle. Therefore, the interaction of TGS1 with UsnRNP proteins SmB/B0 and D1 as well as with the SMN complex appears to correlate with the ordered process of ribonucleoprotein particles assembly and subsequent cap hypermethylation [9]. Borg et al. [10] highlighted that TGS1 is required for normal motor behavior and neuromuscular activity, and that its disruption induces phenotypes that mirror spinal muscular atrophy, a neuromuscular disorder, resulting, in the majority of cases, from insufficient levels of the ubiquitously-expressed survival motor neuron (SMN) protein. TGS1 was detected within a selection signature in cattle with various **indicine introgression** levels [4].

LYN (LYN Proto-Oncogene, Src Family Tyrosine Kinase) encodes a non-receptor tyrosine protein kinase belonging to the Src family tyrosine kinases (SFK). Src family kinases interact with many cellular cytosolic, nuclear and membrane proteins, modifying these proteins by phosphorylation of tyrosine residues. As such, SFKs are involved in the modulation and regulation of many different processes such as proliferation, differentiation, migration, metabolism and apoptosis, responses to DNA damage and genotoxic agents. In **melanoma**, LYN was shown to play an oncogenic role by its contribution to the regulation of cell proliferation, migration, invasion, apoptosis and autophagy via the PI3K/Akt pathway [11]. Pro-oncogenic activity of LYN was also observed in gastric cancer cells [12] where LYN knockdown was found to induce apoptosis and inhibit both migration and invasion. LYN knockdown resulted in the activation of the mitochondrial apoptotic pathway. Likewise, the **Wnt/β-catenin pathway** was inactivated by LYN knockdown and epithelial-mesenchymal transition mesenchymal markers (including N-cadherin and vimentin) were also found to be downregulated. Finally, the AKT/mTOR pathway was found to be downregulated by LYN knockdown in gastric cancer cells.

It has been shown to interact and induce autophosphorylation of **KIT**, to play a role in the control of KIT expression, to change intracellular localization in response to stimulation of the receptor tyrosine kinases, ALK and KIT and to be involved in endosomes and lipid rafts [13]. It has also been shown to activate a variety of signaling components including Jnks, Erks, PI3K, the JAK-STAT pathway [14]. It was demonstrated to be involved in the NF-κB pathway [15,16]. Inhibition of Src-family kinases was shown to impaire phosphorylation and accumulation of c-Jun, leading to reduced formation of AP-1 complexes upon LPS stimulation [17].

LYN has been shown to be activated via cell detachment through decreased membrane cholesterol levels during the change in its membrane distribution [18]. Furthermore, cholesterol incorporation was shown to decreases LYN activity, suggesting that the localization and the function of the Src-family kinase LYN are critically regulated by its membrane anchorage through lipid modifications. Cholesterol, a major component of the plasma membrane, determines the physical properties of biological membranes and plays a critical role in the assembly of membrane microdomains. Enrichment or deprivation of membrane cholesterol affects the activities of many signaling molecules at the plasma membrane. Cell detachment changes the structure of the plasma membrane and influences the localizations of lipids, including cholesterol [19].

In dendritic cells, the membrane raft-associated LYN Src family kinase is used by CD40, whose receptors associate with sphingolipid- and cholesterol-rich plasma membrane microdomains, to initiate CD40 signaling via tyrosine phosphorylation of intracellular substrates, activating a pathway implicating ERK activation and cytokines (interleukins) production [20].

Also, LYN has been shown to be activated by ligand binding to the neutral glycosphingolipid lactosylceramide, that has been shown to form lipid rafts (membrane microdomains) coupled with the Src family kinase LYN on the plasma membranes of human neutrophils. LYN activation in neutrophils was associated with neutrophil functions, such as superoxide generation and migration [21].

A role for LYN and glucosylceramides in the migratory activity of immortalized human endometrial stromal cells has also been shown [22].

Cleavage of LYN during induction of apoptosis may represent another mechanism for the regulation of the Src kinase [23]. Notably, expression of the caspase-cleaved form of LYN (LynDeltaN) in mice was shown to mediate a chronic inflammatory syndrome resembling psoriasis, altering NF-kB activity [24]. In B cells, the mitochondrion-dependent caspase-mediated cleavage of LYN impair apoptosis likely through the modulation of c-Myc expression [25].

In oligodendrocytes, knockdown of LYN resulted in apoptosis with concomitant accumulation of C(16)-ceramide due to activation of acid sphingomyelinase (ASMase) and sphingomyelin hydrolysis. Thus, LYN kinase was suggested to promote cell survival by suppressing acid sphingomyelinase activity [26].

LYN has been shown to be a mediator of epithelial-mesenchymal transition in breast cancer [27] and to regulate epithelial-mesenchymal transition in mice treated with cigarette smoking extracts, through Smad2/3 signaling [28].

Also, LYN has been shown to be involved in radiation-induced signal transduction [29] and to regulate the cell death response to ultraviolet radiation through c-Jun N terminal kinase-dependent FAS ligand activation [30]. It has been shown to be among the intracellular signaling molecules activated by genotoxic stresses, playing a role in regulating DNA damage-induced apoptosis [31].

The Golgi-associated LYN tyrosine kinase has been involved in the translocation of annexin II to the endoplasmic reticulum under oxidative stress [32]. Various findings indicate that Src family members interact in a regulated manner with the cytoskeleton [33]. LYN has been shown to interact with phosphoproteins which regulate cell cycle and the cytoskeleton [34] and is involved in phagocytosis. In glioblastoma cells, under nutrient-deprived conditions, constitutively-active LYN expression enhanced enhanced AMPK activity and survival and promoted autophagy as well as inhibiting cell death and promoting proliferation while expression of dominant-negative LYN promoted cell death. The observed findings suggest that on nutrient deprivation in vitro, as well as in xenograft tumors in vivo, LYN acts to enhance the survival of glioblastoma cells by promoting autophagy and proliferation as well as inhibiting cell death [35]. LYN has been shown to be involved in the polarization of neurons, with the differentiation of axons and dendrites [36]. It was shown to contribute to coordination of motor activity in the brain through regulation of the pathway of N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor [37] and to be among the signals possibly controlling migration and differentiation of the neural crest cells during development [23]. LYN mutations have been implicated in the ability by estrogen receptor-positive breast cancers to adapt to **estrogen** deprivation and become resistant to antiestrogen therapy [38]. Exposure of differentiating human osteoclasts to 17β-estradiol induced upregulation of LYN. In control condition, estrogen treatment increased the apoptosis rate and suppressed the calcium signaling, resulting in reduced osteoclastogenesis. These osteoclasts were smaller in size with reduced extent of multinuclearity and produced significantly low levels of bone resorbing enzymes. They also exhibited

disrupted sealing zone formation with low podosome density, impaired cell polarization and reduced resorption of dentine slices. In LYN knockdown condition, estrogen failed to induce apoptosis. LYN knockdown osteoclasts did not show reduction in production of bone resorbing enzymes and had defined sealing zone formation with high podosome density with no impairment in cell polarization. Thus, the inhibitory action of estrogen on osteoclast was severely restrained in LYN knockdown condition, demonstrating the importance of LYN as a key mediator of the effect of estrogen on osteoclastogenesis [39]. LYN tyrosine kinase expression was shown to be upregulated in castrate-resistant prostate cancer compared with normal tissue. Castrate-resistant prostate cancer progression is a complex process by which prostate cells acquire the ability to survive and proliferate in the absence or under very low levels of androgens. Most castrate-resistant prostate cancer tumors continue to express androgen receptors as well as androgen-responsive genes owing to reactivation of androgen receptors. LYN expression in castrate-resistant prostate cancer was shown to enhance androgen receptor transcriptional activity while targeting LYN kinase was shown to induce dissociation of androgen receptors from the molecular chaperone Hsp90, leading to their ubiquitination and proteasomal degradation, indicating a mechanism of regulation of androgen receptor stability and transcriptional activity by LYN [40]. Finally, LYN was detected within a selection signature in cattle with various **indicine introgression** levels [10].

CHCHD7 (Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 7) encodes a protein of the mitochondrial intermembrane space, which is a member of the CHCH-containing twin CX9C proteins [41]. This protein functions in mitochondrial copper homeostasis and is essential for the expression of functional cytochrome oxidase [42]. Mitochondria are cellular organelles that are essential to aerobic ATP production and, as such, energy homeostasis. ATP is generated by the coordinate activity of five multimeric enzyme complexes, most of which rely on iron–sulfur, heme, or copper centers for their catalytic competence. Mitochondria therefore have a vested interest in the cellular metabolism of metal ions. It is perhaps not surprising then that bioactive pools of several metals, including iron and copper, are localized to the mitochondrial matrix, and are crucial to the sustained synthesis and delivery of prosthetic groups that are required by these enzymes for their assembly and proper function. As mitochondria contain bioactive pools of copper and iron, mechanisms must exist to acquire, store, and mobilize these elements. Many of the proteins that mediate the uptake of iron into mitochondria and its subsequent assimilation into heme and iron–sulfur clusters have been identified; however, those critical to mitochondrial copper metabolism remain unknown. What is clear is that copper export from the matrix to the mitochondrial intermembrane space is required for its use in metallating cytochrome c oxidase (COX) subunits I and II during the biogenesis of COX, and in maturing the small fraction of the total cellular copper–zinc superoxide dismutase (SOD1) that resides in this compartment. Delivery and insertion of copper into each of these enzymes is surprisingly complex. To date, 12 accessory proteins with essential roles in the maturation of COX, SOD1 or both enzymes have been identified in yeast. Each factor has a human orthologue and contains highly conserved cysteines that are organized as Cx3C or Cx9C motifs. While it is known that these motifs are used to oxidatively trap soluble accessory proteins within the mitochondrial intermembrane space, thereby ensuring their appropriate localization, most of these proteins have yet to be functionally characterized. However, studies of COX17, SCO1, and SCO2 in a number of in vivo and in vitro systems have provided robust evidence that redox regulation of their cysteine residues is

crucial to their metallochaperone functions. Data also support an important role for redox regulation of the copper-binding cysteines of SCO1 in the transduction of a SCO-dependent, mitochondrial signal that modulates cellular copper homeostasis [43].

It was detected within a number of selection signatures studies and GWAS for body weight and milk characteristics in cattle [44], bovine stature [45], carcass meat yield [46], carcass weight and stature in Japanese Black cattle [47], weight gain and carcass traits in Japanese Black steers [48], birth weight in indicine (Nellore) cattle [49], knuckle, biceps and shank weight in Simmental beef cattle [50], beef quality traits in Angus cattle [51] as well as in a selection signature in cattle with various **indicine introgression** levels [4].

SDR16C5 (Short Chain Dehydrogenase/Reductase Family 16C Member 5, alias RDHE2, epidermal retinol dehydrogenase 2) encodes a member of the short-chain alcohol dehydrogenase/reductase superfamily of proteins and is involved in the oxidation of retinol to retinaldehyde [52], one of the steps necessary for conversion of retinol into retinoic acid, the major bioactive form of vitamin A, which influences a broad spectrum of physiological processes during embryogenesis and adulthood, regulating, through interactions with nuclear transcription factors, the retinoic acid receptors, the expression of over 500 genes. Diseases associated with SDR16C5 include psoriasis. Interestingly, by screening key genes and possible signaling pathways involved in the **differentiation and proliferation of human melanocytes**, Mei et al. [53] found SDR16C5, as well as the DHRS3, DHRS9, and RDH10 genes in retinol metabolic pathway, continuously down-regulated at different culture time points, suggesting that the differentiation and proliferation of melanocytes may be accompanied by an increase in the expression of genes involved in retinoic acid catabolism and a decrease in the expression of synthesis-related genes. As a result, the catabolism of retinoic acid may contribute to the differentiation, proliferation and maturation of cultured melanocytes. Wu et al. [54] showed that mice lacking the epidermal retinol dehydrogenases SDR16C5 display accelerated **hair growth**. A role for retinoic acid signaling in **melanoma** cell lines has been reported by Epping et al. [55] (see Supplementary file S1). Retinoic acid has been shown to work as a **morphogen** in embryos [56]. Deletion of the Notch pathway co-factor RBP-J in mouse hair follicle stem cells was shown to trigger adjacent melanocyte stem cells to precociously differentiate in their shared niche. Transcriptome screen and in vivo functional studies revealed that the elevated level of retinoic acid caused by de-repression of retinoic acid metabolic process genes as a result of RBP-J deletion in hair follicle stem cells triggers ectopic **melanocyte stem cells differentiation in the niche**. Hence, RBP-J functions as a repressor in hair follicle stem cells to suppress retinoid metabolic process genes and consequently the level of retinoic acid in the niche shared by hair follicle stem cells and melanocyte stem cells. Elevated levels of retinoic acid were shown to be both necessary and sufficient to induce ectopic **melanocyte stem cells pigmentation in the niche** in hair cycle dependent fashion, as well as to lead to increased level of c-Kit protein on melanocyte stem cells. The increased level of c-Kit on melanocyte stem cells was shown to be required for their ectopic differentiation and this phenomenon occurred via the c-Kit-MEK pathway. The study showed that it is the KIT-ligand originated from hair follicle stem cells that activates the c-Kit-MEK pathway to induce melanocyte stem cells ectopic differentiation in the mutant niche. Overall, melanocyte stem cells were shown to maintain self-renewal ability by expressing low level of c-Kit to remain insensitive to the differentiation signals. Their neighboring hair follicle stem cells are not just passive receiver of signaling inputs from the niche, as they actively suppress

differentiation-sensitizing signals in the niche, such as retinoid acid level, to help maintain a differentiation refractory niche environment [57]. The addition of retinoic acid to the medium was shown to significantly decrease the proliferation of normal human adult epidermal melanocytes as well as of human undifferentiated epidermal melanoblasts, in a dose-dependent manner. It also significantly decreased both MITF and TRP-1 mRNA expression level in normal human adult epidermal melanocytes while MITF and TRP-1 mRNA expression levels in human melanoblasts were significantly increased following the addition of retinoic acid, thus suggesting that **retinoic acid has significantly different effects on melanocytes depending on their stage of differentiation**. More specifically, **retinoic acid promotes differentiation in earlier stages, in which embryonic stem cells become melanoblasts via neural crest cells, and inhibits differentiation in later stages, in which melanoblasts become melanocytes**. EDNRB was suggested as the key molecule involved in the mechanism of retinoic acid in human melanocytes [58]. It was detected within a GWAS for birth weight in indicine (Nellore) cattle [49] as well as in a candidate region for differential selection by contrasting three Korean cattle breeds displaying **different coat color phenotypes** [3].

SDR16C6 (Short Chain Dehydrogenase/Reductase Family 16C Member 6) Pseudogene

PENK (Proenkephalin) is an endogenous opioid polypeptide hormone and a negative regulator of cell proliferation and tissue organization. A number of immunocytochemical and biochemical studies have shown that the peptides are concentrated heavily in the **hypothalamus** of various species. All hypothalamic structures except the mammillary bodies have been shown to contain PENK neurons. The massive numbers of PENK neurons throughout hypothalamic structures suggest that PENK neurons participate in numerous homeostatic functions. However, the chiasmatic region has the greatest number of neurons, especially in the intermediate nucleus, but also in the suprachiasmatic nucleus and scattered throughout the medial and lateral preoptic regions. There was also robust labeling of neurons by the pre-PENK probe in the bed nucleus of the stria terminalis and in the central nucleus of the amygdala. Several of these hypothalamic structures have been reported to be **sexually dimorphic** [59]. High levels of PENK mRNA and PENK-derived peptides are expressed in embryonic mesenchymal tissues during differentiation into mature tissues and organs. Shortly after birth, as development progresses, PENK expression drops in those tissues to undetectable levels [60]. In the rat cardiac muscle, PENK was shown to rise five- to six-fold between 3 and 27 months of age. Elevated levels of peptide and mRNA in the aging heart suggest that enkephalins contribute to age-associated cardiac adaptations [61]. PENK is processed through the action of proprotein convertase (PC)1and PC2 to produce the enkephalin peptides, met-enkephalin and leu-enkephalin. Opioid peptides act on specific opiate receptors found on nervous and mucosal cells, and on various cells in the immune system. They link the neuroendocrine and immune systems to control immunological functions. The receptors for enkephalins include mu, delta and kappa opioid receptors, which are expressed on skin cells, and their activation **can regulate keratinocyte and melanocyte activities**. There is evidence that the endogenous opioids modulate stress-induced effects, including environmental stresses such as **solar radiation**, antigenic stimuli, and physical, chemical and biological insults. The skin responds to these insults through complex biological and biochemical activities, including PENK, which is coordinated by local neuroendocrine and immune systems [62]. Reactive oxygen species (ROS) were

shown to dramatically induce the expression of the opioid proenkephalin (PENK) in primary astrocytes [63]. Following acute stress, PENK transcription was shown to increase in the swine caudate putamen at the base of the forebrain [64]. It was detected as a differentially methylated gene by comparing prenatally stressed with non-stressed young Brahman bull calves [65]. Mild maternal undernutrition in early pregnancy was shown to induce greater levels of PENK mRNA in restricted fetuses [66]. PENK is a Hedgehog-responsive gene [67]. **It belongs to the opioid/orphanin gene family, together with, prodynorphin, nociceptin/proorphanin and proopiomelanocortin**, the latter being a complex precursor that comprises several peptidic hormones, including **melanocyte-stimulating hormones** (MSHs), adrenocorticotropic hormone (ACTH), and β-endorphin [68]. It has been included in the Immediate-Early Genes group, that includes genes for which the activation of transcription is fast (within minutes) and transient after a given cellular stimulus and undetectable in quiescent cells. Immediate-Early Genes do not require de novo protein synthesis to be activated and are grouped into 'regulatory transcription factors' and 'effector factors. PENK expression was shown to be suppressed in neural crest derived cells by CaMK2 antagonist [69]. See Supplementary file S2 for the function of CAMK2B. The expression of PENK has been shown to be increased by pituitary adenylate cyclase activating peptide38 (PACAP38), i.e., a neuropeptide of the secretin-glucagon-VIP superfamily [70]. Also, PENK has been shown to be regulated by PKA, PKC and tyrosine kinases [71,72], and glutamate receptors of the NMDA type were involved in the maintenance of the expression of the PENK gene in neostriatal neurons [73] and in the neocortex [74]. PENK expression has been found to be **increased in keratinocytes in psoriatic skin, suggesting a role for PENK in the pathogenesis of the skin disease** [72]. PENK depletion substantially derepresses transcription of a range of antiapoptotic gene targets previously implicated in repression-mediated apoptosis induction by NF-κB and p53. It has been hence suggested to assist stress-activated apoptosis through transcriptional repression of NF-kappaB- and p53-regulated gene targets [75] and to be differentially expressed in cell lines with different sensitivity to a small organic molecule that has been shown to restore tumor-suppressor function to mutant p53 [76]. In osteosarcoma, PENK was shown to promote cell migration by regulating the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway [77]. CpG sites in the PENK gene have been frequently reported in DNA methylation studies investigating **aging-associated changes** [78-81]. Evidence gathered from neurochemical and pharmacological studies point to an important role of opioid peptides in the balanced and/or coordinated activity of the brain striatal output pathways in pathological conditions such as Parkinson's disease [82,83]. PENK expression in an in vitro model of Huntington's disease, a polyglutamine neurodegenerative disorder, comprised of primary striatal neurons expressing N-terminal fragments of mutant huntingtin reproduced the gene expression pattern seen in human Huntington's disease [84]. PENK was upregulated after neurogenic induction of bone marrow mesenchymal stomal cells and was involved in synaptic transmission/long term potentialization [85]. In cultured neocortical interneurons, endogenous glutamate enhanced N-methyl-D-aspartate-induced gene expression by acting via Group I metabotropic glutamate receptors. In contrast, stimulation of Group I metabotropic glutamate receptors by endogenous glutamate decreased the CREB phosphorylation and PENK gene expression induced by the activation of (S)-α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid receptors [86]. Steroids, including glucocorticoid, the major mammalian response to stress, are associated with the regulation of the PENK gene. PENK gene expression was shown to be regulated by

glucocorticoids via a mechanism that varies with age and tissue and functions during the induction of the Penk gene and not to maintain the basal gene expression [87]. In turn, PENK has been shown to represent a possible stimulatory input for ACTH release [88]. Cortisol has been suggested to play an important role in the regulation of fetal adrenal PENK mRNA levels and enkephalin synthesis by the adrenal gland of the fetal sheep [89]. Enkephalin levels are responsive to gonadal **steroids** [90]. PENK was identified among the genes that were significantly regulated during progesterone-induced endometrium maturation [101]. Proenkephalin mRNA was shown to be regulated by 17 beta-estradiol in the endometrium and this effect of estradiol was antagonized by progesterone. Borthwick et al [102] and Carson et al [103] also found decreased endometrial expression of PENK during the secretory phase using microarray analysis. Differential expression of PDYN and PENK during the estrus cycle generally correlates with distinct differences in the degree of colocalization of estrogen and progesterone receptors mRNA in PDYN and PENK mRNA-containing neurons in the anteroventral periventricular nucleus of the preoptic region, which represents an essential component of neural pathways regulating gonadotropin secretion, and contains sexually dimorphic populations of neurons that express dynorphin or enkephalin [104]. All three major classes of endogenous opioid peptides have been implicated in mediating the actions of estrogens and progesterone on GnRH release. Sex- and steroid-associated differences in enkephalin neurons in the ovine paraventricular nucleus have been reported and suggest that opioid peptides may have an important role in the control of LH release. In rodents, enkephalin neurons have been shown to project to GnRH neurons in the preoptic area, further supporting a role for these neurons in the control of the reproductive axis [105]. The authors confirmed that the inhibitory actions of progesterone are associated with an increase in opioid gene expression in specific hypothalamic nuclei. An increase in progesterone was associated with increased POMC gene expression in the arcuate nucleus and increased PENK expression in the paraventricular nucleus. In addition to androgen receptors (ARs) and testosterone, opioid neuropeptides in the medial preoptic nucleus influence sexually-motivated song production in male European starlings, and it has been proposed that testosterone may in part regulate song by modifying opioid systems. Results support the hypothesis that ARs may alter opioid gene expression in medial preoptic nucleus to fine-tune singing to reflect a male's motivational state [106]. A substantial proportion of the PENK-expressing cells in the anterior part of the mice medial preoptic area were positive for estrogen receptor α and androgen receptor and may hence be sensitive to gonadal steroid hormones [107]. PENK was detected within a GWAS for birth weight in indicine (Nellore) cattle [49], for body measurement traits in Chinese Wagyu beef cattle [108]. In a whole-genome gene expression study that compared **prepubertal and postpubertal** Brangus (**Bos indicus-influenced composite cattle**) heifers, PENK was one of the most differentially expressed genes, with its expression being higher in post-puberty heifers in five tissues: uterus, endometrium, hypothalamus, pituitary gland, and live [109]. In sheep, increased progesterone was associated with increased POMC and PENK gene expression [105], with increased progesterone levels occurring in the transitional peripubertal phase before mature estrus cycles and fertility are achieved [110]. The PENK locus has been also detected in several GWAS-QTL efforts involving Bos **indicus-influenced cattle** in Australia and the United States [111,112]. This locus was also found to be a QTL in GWAS of bull fertility traits also indicative of puberty in Brahman bulls, which are a Bos indicus breed [111]. This gene was also reported to be differentially expressed in the pituitary gland of Brangus heifers [113,114]. Finally, PENK was

validated in a tropical composite cattle population, as a marker for sexual precocity traits [115].

LOC112449660 Uncharacterized locus

IMPAD1 (Inositol Monophosphatase Domain-Containing Protein 1, alias 3'(2'), 5'-Bisphosphate Nucleotidase 2, BPNT2, alias IMPase) encodes a member of the inositol monophosphatase family. Is a Golgi-resident phosphatase responsible for the hydrolysis of phosphoadenosine phosphate (PAP), the byproduct of sulfotransferase reactions, to adenosine monophosphate (AMP). Sulfur is an essential element in all life forms used in the synthesis of sulfur-containing amino acids, maintenance of cellular redox states and detoxifying toxic compounds. 3'-phosphoadenosine 5'-phosphosulfate (PAPS) is the active form of sulfur used in these reactions, which consume PAPS, producing 3'-phosphoadenosine 5'-phosphate (PAP). PAP is degraded to 5′-AMP (AMP) by 3′-nucleotidase family. Mammals encode two 3′-nucleotidases, the Golgi-resident inositol monophosphatase 3 (IMPAD3 aka PAP phosphatase, gPAPP) and the cytosolic bisphosphate 3′-nucleotidase 1 (BPNT1, described in its own reac tion). Both require Mg2+ as cofactor and both are inhibited by lithium [116]. BPNT2 drives the sulfation of glycosaminoglycans, which are then secreted from the Golgi and form the cartilaginous extracellular matrix. In humans, loss-of-function of the enzyme is associated with diseases involving bone deformities, and chondrodysplasia. IMPAD1 inactivation in mice has been shown to produce chondrodysplasia with abnormal joint formation and impaired proteoglycan sulfation. The human chondrodysplasia associated with IMPAD1 deficiency joins a growing number of skeletoarticular conditions associated with defective synthesis of sulfated proteoglycans, highlighting the importance of proteoglycans in the development of skeletal elements and joints [117].

Glycosaminoglycans which are major constituents of the cell surface and extracellular matrix, but are also found in intracellular compartments, are believed to be important in modifying the growth of cells both in vitro and in vivo. These molecules may be involved in the adhesion of cells to each other and to the substratum or membranes. Several examples of the role of **glycosaminoglycans** (such as dermatan sulfate, keratan sulfate, chondroitin sulfate and heparan sulfate) **in pigment biology** and pathology are available in the literature, briefly and un-exhaustively addressed in what follows.

Dermatan sulfate has been shown to be required for **neural crest cells to migrate** and adhere to fibronectin [118]. A decline in the proportion of hyaluronic acid was found in pigmented cultures obtained from neural crest cells, possibly related to pigmentation. The overall pattern of glycosaminoglycans synthesis by melanocytes differentiated in vitro was relatively enriched in sulfated glycosaminoglycans, as is the environment that they colonize in vivo [119]. Whereas both **melanocyte and melanoma** cultures were shown to produce hyaluronic acid, chondroitin 4-sulfate, and heparan sulfates, with quantitative differences between the two cell cultures, only the melanocyte culture produced chondroitin 6-sulfate [120]. Melanoma cells were confirmed to present an altered glycosaminoglycan profile compared to that of melanocytes [121,122]. In metastatic melanoma, amount and composition of glycosaminoglycans are altered compared with nonmetastatic melanoma, indicating their involvement in melanocytic tumor progression [123,124]. Treatment of human metastatic melanoma cells with fibroblast growth factor-2 (FGF-2) was shown to strongly reduce the expression levels of the heparan sulfate-containing proteoglycan, syndecan-4, a focal adhesion component in a range of cell types, and to significantly enhance migration ability [125].

Cultured keratinocytes were shown to produce substantially more sulfated glycans than do the melanocytes; heparan sulfate was shown to be quantitatively the major sulfated glycosaminoglycan of keratinocytes and chondroitin sulfate the major product of melanocytes; during the transition from active growth to growth inhibition, heparan sulfates as proteoglycans and free chains increased in keratinocyte cultures, whereas no such transition was apparent for the melanocyte heparan sulfates; total production of chondroitin sulfate proteoglycans was down-regulated in both cell lineages with growth inhibition. The contrasts suggested that the synthetic patterns have evolved divergently as the two cell types exploited proteoglycans differently for regulating molecular pathways of growth and differentiation [126,127] cultured mouse neural crest cells in the presence of stem cell factor (SCF) in individual wells coated with extracellular matrix (fibronectin, collagen I, chondroitin sulphate, dermatan sulphate). More KIT-positive cells and DOPA-positive cells were detected in the presence of SCF on ECM-coated wells than on non-coated wells. A statistically significant increase in DOPA-positive cells was evident in fibronectin and collagen I wells. In contrast, in the absence of SCF, few DOPA-positive cells and KIT-positive cells were detected on either the ECM-coated or non-coated wells. The authors concluded that ECM affect **melanocyte proliferation and development** in the presence of SCF. Cell adhesion studies on micropatterned surfaces on silanised glass substrate, obtained through a photo-immobilisation procedure, highlighted that the sulphated hyaluronan derivative is capable to stimulate melanocyte proliferation when added to the culture medium more than the native hyaluronan polysaccharide. Melanocytes adhered on the sulphated hyaluronan derivative coated stripes while on the hyaluronan-coated micropatterned surfaces they spread around the structured area, resulting in the exclusion of the topographic pattern [128].

Takabe et al. [129] highlighted that melanocytes carry a thick and dynamic hyaluronan coat and that the **UVB-induced expression of proinflammatory mediators in melanocytes** depends on this coat. Removal of the pericellular hyaluronan coat by hyaluronidase further promotes the expression of the proinflammatory mediators in UVB-exposed melanocytes. The signaling pathways leading to the up-regulation of the studied cytokine and chemokines depends on the activation of TLR-4, p38, and NF-kB. Heparin, a highly sulfated glycosaminoglycan and an analogue of heparan sulfate chains of proteoglycans, frequently used for exploring the role of heparan sulfate in binding and interacting with various growth factors, chemokines, extracellular matrix proteins, and enzymes, was shown to interfere with keratinocyte phagocytosis through blocking PI3k/Akt and MEK/ERK signaling pathways, suggesting that heparin may serve as a potent antiphagocytic and anti-inflammation agent in epidermis [130].

In the context of cancer, IMPAD1 undergoes mRNA upregulation and is co-amplified with oncogenes like MYC. Bajaj et al. [131] identified previously unknown functions of IMPAD1 in enhancing Golgi-mediated secretion of matrix metalloproteases (MMPs) to drive cellular invasion and metastasis. A role of IMPAD1 in promotion of lung cancer metastasis has been proposed by Yang et al. [132] who showed it mediated metastasis through mitochondria dysfunction by inhibiting mitochondrial Complex I activity to reduce ROS production, leading to AMPK phosphorylation, which in turn induced Notch1-mediated upregulation of HEY1. The gene expressions of IMPAD1 (gPAPP) and BPNT1 were shown to be remarkably down-regulated in glioma. IMPAD-1 hydrolyzes the Golgi PAP yielding AMP and phosphate, BPNT-1 hydrolyzes cytoplasm PAP to AMP and phosphate. Therefore, it is reasonable to speculate that the deficiencies of IMPAD1 and BPNT1 function would lead to a lower

degradation rate of PAP and hence promote its accumulation in glioma [133]. IMPAD1 was found in a genome-wide association study on body measurement traits in Chinese Wagyu beef cattle [108].

Inhibition of the IMPAD1 paralog, BPNT1, in the nervous system, can cause selective toxicity to specific neurons [134]. In Caenorhabditis elegans, activity of XRN2, a conserved 5′→3′ exoribonuclease that recognizes RNA with a 5′ monophosphate and degrades it to mononucleotides, is promoted by BPNT1 through hydrolysis of the endogenous XRN inhibitor, PAP [135]. Mice lacking BPNT1 develop iron deficiency anemia, due to accumulation of PAP. The anemia is rescued in BPNT1 null mice harboring hypomorphic mutations in PAPSS2 (3'-Phosphoadenosine 5'-Phosphosulfate Synthase 2) causing decreased PAP metabolic toxicity [116,136]. In mice lacking BPNT1 at the level of the intestinal epithelium, tissue specific metabolic toxicity (elevated PAP levels in the duodenal epithelium) was observed, that cause reduced expression of key iron homeostatic genes involved in dietary iron reduction via duodenal cytochrome reductase, apical iron import, transcriptional coordination of iron regulatory genes, and iron export to the blood via ferroportin. Inhibition of intestinal BPNT1 was identified as a strategy to overcome hemochromatosis in mice. The study provided insights into the role of sulfur assimilation metabolism in mediating disorders of iron deficiency and overload in mice [137], with a role of iron in **pigmentation** being known.

BPNT1 was found in a genomic region associated with **puberty** traits segregating across tropically adapted cattle breeds [115].

Other paralogs of this gene are INPP1, which encodes an inositol polyphosphate-1-phosphatase, one of the enzymes involved in phosphatidylinositol signaling pathways, IMPA1, which encodes the inositol monophosphatase 1, that dephosphorylates myo-inositol monophosphate to generate free myo-inositol, a precursor of phosphatidylinositol, and is therefore an important modulator of intracellular signal transduction via the production of the second messengers myoinositol 1,4,5-trisphosphate and diacylglycerol, and IMPA2, encoding the inositol monophosphatase 2, that catalyzes the dephosphoylration of inositol monophosphate and plays an important role in phosphatidylinositol signaling.

In the phosphatidylinositol signaling pathway, activated phospholipase C (PLC) by the binding extracellular signal molecule to the receptor on the cell surface catalyzes the hydrolysis of phosphatidylinositol-(4,5)-bisphosphate (PIP2) into two secondary messengers IP3 (inositol triphosphate) and (diacylglycerol) DAG, which both convert extracellular signal into intracellular signal. The derived phosphoinositides are involved in many signaling pathways such as the PI3K-Akt pathway that mediates cell proliferation, survival, and metabolism. In addition, phosphoinositide signaling also mediates many cell activities like cell migration, endocytosis, membrane dynamics.

PI3K pathway and its effects on **melanocytes** have been addressed in various studies [138]. In particular, Mosca et al. [138] showed that αMSH-dependent PI3K/AKT signaling play a key role in the control of both **melanogenesis** and **extracellular release of pigment**.

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