Supplementary Information

Full description of POP landscape depicted in Figure 1

In the description of the landscape below, all candidate genes/proteins that were implicated in POP through our exome chip study (**Table 2**), the other POP candidate genes/proteins/molecules (**Supplementary Table 1**), and three POP-linked signaling molecules (estradiol, glutathione and progesterone) are indicated in bold.

Signaling through the molecular landscape is initiated at the cell membrane of epithelial cells and underlying fibroblasts of the urogenital tract, where the binding of ligands from the extracellular matrix (ECM) to their respective receptors leads to the modulation of several downstream molecular cascades in the cytoplasm, cytoskeleton, endoplasmic reticulum and nucleus. These cascades converge on regulating epithelial-mesenchymal transition (EMT). In essence, EMT is characterized by a so-called 'cadherin switch' that is initiated when epithelial cells start producing less of the epithelial marker and membrane protein **E-cadherin (CDH1)** and more of the mesenchymal marker N-cadherin (CDH2) (not shown)[1]. This in turn results in the adherens junctions between epithelial cells letting loose and the epithelial cells gradually transforming into mesenchymal cells.

In normally functioning epithelial cells, cytoplasmic **AHNAK** binds and stabilizes the epithelial cytoskeleton, which in turn results in **CDH1** being anchored to and modulated by the (actin) cytoskeleton. Cytoskeleton-anchored **CDH1** of opposite cells bind each other and hence positively regulate epithelial cell-cell contacts, preventing EMT[2,3]. Further, **NEB** binds and stabilizes the (actin) cytoskeleton[4], the organization of which is also regulated by cytoplasmic **ARHGEF19**[5], which is itself upregulated by the extracellular cytokine **TGF-beta-1** (**TGFB1**)[6]. **TGFB1** is a key positive regulator of EMT as it significantly downregulates **CDH1** expression[7]. In this respect, **SCUBE2** is an ECM protein that is involved in upregulating the expression of **CDH1**, and hence inhibits **TGFB1**-induced EMT[8]. Furthermore, **AHNAK** shuttles between the cytoplasm and nucleus[9], and nuclear **AHNAK** can *induce* EMT[2]. A possible explanation for the role of **AHNAK** in inducing EMT may lie in the fact that in response to **TGFB1**, **AHNAK** promotes the activation and translocation of **SMAD3** to the nucleus[10], which in turn downregulates **CDH1**[7].

In addition and as further described below, **SMAD3** regulates the expression of a number of EMT-involved extracellular proteins. ZFYVE9 (other name: SARA) is a peptidase that binds and retains **SMAD3** in the cytoplasm. Upon phosphorylation and activation by **TGFB1** (see above), phosphorylated **SMAD3** translocate to the nucleus and promotes EMT[11,12]. Further, ZFYVE9 binds and forms a functional complex with the endoplasmic reticulum (ER) membrane-located **ANKLE2**[13], and inhibits EMT through upregulating the expression of **CDH1**[14]. **TGFB1** is additionally involved in modulating the **SMAD3**-ZFYVE9-**ANKLE2** complex through downregulating the expression of ZFYVE9[14] and regulating **ANKLE2** expression[15].

Within epithelial cells, the activation and translocation of **SMAD3** to the nucleus is also positively regulated by the adaptor protein NFKB[16]. In turn, NFKB is activated by cytoplasmic **FASTKD1** and **RRM2**[17,18], and downstream of **TGFB1** signalling[19]. Furthermore, **SMAD3** and **TGFB1** upregulate each other's expression[20,21]. When activated in the nucleus by e.g. **AHNAK** (see above), **SMAD3** downregulates the expression of the nuclear estrogen receptor **ESR1**[22]. In turn, through binding and forming a complex with its natural ligand, the female sex hormone **estradiol (E)**, **ESR1** upregulates the expression of **AHNAK**[23,24]. The POP-implicated microRNAs **miR-221** and **miR-222** also negatively regulate **ESR1** expression through binding and destabilizing the **ESR1** mRNA[25]. Epithelial[26] **NOP56** also binds and interacts with estradiol-bound **ESR1**[24]. Moreover, **USP4** is an enzyme that deubiquitinates ADORA2A - an epithelial and mesenchymal receptor that is bound and activated by extracellular adenosine (A)[27] - which increases the amount of functional receptors at the cell membrane[28]. The A-ADORA2A complex is also involved in upregulating the expression of **CDH1**[29] and hence inhibiting EMT[30] (see above). Further, **STYK1**, a membrane protein that is upregulated downstream of **SMAD3**[31], promotes EMT through decreasing **CDH1** expression[32].

Apart from downregulating **ESR1** and **CDH1** (see above), nuclear **SMAD3** upregulates the expression of the other nuclear estrogen receptor **ESR2**[22]. Further, **E**-bound **ESR1** and **ESR2** upregulate and downregulate the expression of **PGR** - the nuclear receptor for the pregnancy hormone **progesterone (P)** - respectively[33]. Interestingly, through our exome chip analysis, we identified POP patients with mutations in the genes encoding **AKR1C1** and **AKR1D1**, two functionally related enzymes that negatively regulate the production of **P** through promoting its conversion into inactive **P** metabolites[27]. **P**-activated **PGR**[34] and **E**-activated **ESR2**[35]

upregulate the expression of **GGCT**, one of the major enzymes involved in the metabolism of the important cellular antioxidant **glutathione (G)**[36] that is highly expressed in the nucleus and cytoplasm of epithelial cells of the reproductive system[37]. **GPX1**, **GSTP1** and **METAP1** are other cytoplasmic enzymes with an important role in the production and metabolism of glutathione[27,38]. The membrane protein **RAGE** is the receptor for extracellular **AGE** (or advanced glycation end product) molecules. The **AGE**-**RAGE** complex regulates a number of downstream signaling cascades and is found in both epithelial cells and fibroblasts (see below)[39]. In epithelial cells, **GPX1** is involved in downregulating the expression of **RAGE**[40].

In addition, **GSTP1** is involved in regulating the expression of **ATP12A**[41], a membrane-located symporter of potassium (K+) and hydrogen (H+)[27] that regulates epithelial cell function[42]. Moreover, **E**-bound **ESR1**[43] and **ESR2**[44] as well as **P**-bound **PGR**[45,46] inhibit EMT through upregulating **CDH1** expression, while **extracellular matrix protein 1 (ECM1)** promotes EMT through downregulating **CDH1**[47]. **E**-bound **ESR1** also upregulates the expression of **WNT4**[48], an extracellular regulator of EMT[49] that is downregulated by **TGFB1**[6]. Further, **FBLN3** is an ECM protein that binds and forms a functional complex with **ECM1**[50] and negatively regulates EMT through upregulating **CDH1** expression[51]. In addition, **FBLN3** inhibits **TGFB1**-dependent signaling[52]. Lastly, **SDHAF3** is a mitochondrial enzyme that negatively regulates EMT[53]. In addition, **TFAM** is a mitochondrial enzyme that is highly expressed in epithelial cells[54] and required for maintaining normal levels of mitochondrial DNA (mtDNA)[27]. Interestingly, changes in mtDNA copy number may play a role in POP development[55-57].

A part of the landscape is also involved in regulating the immune response in that beta-2-microglobulin (B2M) - an EMT-inducing[58,59] extracellular protein that mediates the presentation of antigens to the immune system [27]- is (up)regulated by **TGFB1**[60]. Further, B2M binds and functionally interacts with **LILRA1**[61], and it is involved in upregulating the expression of **HLA-DQA1** and **HLA-DQB1**[62], which form a functional complex with each other[63] and are both downregulated by **TGFB1**[62]. **HLA-DQA1** and **HLA-DQB1** are MHC class II (MHC II) proteins[27] . MHC II proteins are expressed in epithelial cells of the female reproductive tract where they are involved in regulating the immune response through presenting foreign antigens to circulating T lymphocytes[64,65] (not shown).

Remodeling of the ECM constitutes another major signaling cascade within the landscape and almost all POP candidate genes identified prior to this study encode proteins that are involved in this process. Further, fibroblasts produce most of these extracellular POP candidates (see below). In addition, literature suggests that in women with and without POP, mechanical stretch alters the response of fibroblasts to ECM remodeling and the interaction between the ECM and these fibroblasts[66-68]. The ECM is composed of different molecules, including **collagen (COL)** and **elastin (ELN)** fibers as well as proteins that crosslink or regulate them. First, A-activated ADORA2A (see above) is involved in upregulating the expression of the extracellular collagen **COL3A1**[69,70] and downregulating the extracellular matrix metalloproteinase **MMP9**[71] - which itself is upregulated downstream of NFKB[72,73] and degrades **COL1A1**[74] and **ELN** [75] - and **TGFB1**[30]. Moreover, the A-ADORA2A complex inhibits the degradation of **ELN**[71] while **MMP9** is involved in upregulating the expression of another collagen, **COL18A1**[76]. **Fibulin 5 (FBLN5)** and **lysyl oxydase oxidase like 1 (LOXL1)** preferentially bind each other[77-79] and the **FBLN5**-**LOXL1** complex facilitates the crosslinking of elastic fibers through binding and interacting with **ELN**[77]. In addition, **lysyl oxidase (LOX)** catalyzes the crosslinking and formation of elastic fibers through **ELN** binding[80-82].

Apart from elastic fiber crosslinking, **LOX** is essential for binding and hence crosslinking collagens such as **COL1A1** and **COL3A1**[83]. **FBLN5** inhibits EMT through significantly enhancing the ability of **TGFB1** to downregulate the expression of **CDH1**[84](not shown). **FBLN5** also increases the expression of **MMP2**[84] and regulates the activity of **MMP9**[84,85]. **MMP2** is a key MMP in the landscape as it degrades **COL1A1**[74] and **ELN**[86] and is downregulated through estradiol-bound **ESR2**[87] and upregulated by NFKB[88]. Further, **MMP2** is involved in upregulating the other MMPs **MMP1**, **MMP3** - which promotes EMT through degrading **CDH1**[89,90] - and **MMP9**[91].

The extracellular protein **TIMP2** binds and forms a complex with **MMP1**[92] and **MMP2**[93] while it inhibits **MMP1**[94], **MMP2**[95] and **MMP9**[96]. **TIMP1** - a protein that is functionally related to **TIMP2** - inhibits **MMP1**[92], **MMP2**[97], **MMP3**[27,98] and **MMP9**[97], while its expression is upregulated by **TGFB1**[99]. Moreover, **MMP3** activates both **MMP9**[100] and **MMP1**[101], with the latter being upregulated by **ELN**[102]. Both **MMP1** and **MMP3** also upregulate the expression of **MMP9**[103]. Additionally, **COL18A1** downregulates the expression of **MMP1**[104] and inhibits

MMP2[105], which itself is involved in upregulating **COL18A1** expression[106]. Further, **BMP1** is an extracellular matrix metalloproteinase that cleaves and regulates the activity of **LOX**[107]. Likewise, **BMP1** directly binds, interacts with and regulates the activity of **COL1A1** through cleavage[107-109]. Also, **FBLN3** downregulates the expression of **FBLN5**[110] while it negatively regulates **MMP2** and **MMP9**[110]. Lastly, **LAIR2** is another ECM protein that binds and functionally interacts with **COL1A1**, **COL3A1** and **COL18A1**[111].

TGFB1 is involved in ECM remodeling through regulating the expression of the majority of the above described ECM proteins. **TGFB1** mediates collagen and elastin fiber deposition in the ECM through (up)regulating the expression of **BMP1**[112,113], **COL1A1**[114-117], **COL3A1**[116], **ECM1**[15], **ELN**[117], **FBLN5**[84,118], **LOX** and **LOXL1**[117]. Moreover, **TGFB1** upregulates the expression of **MMP2**[119], **MMP3**[119,120] and **MMP9**[119,121] while it is involved in decreasing the expression of **MMP1**[122,123]. In addition, cell surface-localized **MMP2** and **MMP9** can cleave and hence activate latent **TGFB1** (not shown)[124].

The extracellular proenzyme **plasminogen** (**PLG**) is cleaved by the PLAU and PLAT enzymes (not shown) to plasmin (PL)[27], an extracellular enzyme that dissolves the fibrin of blood clots and acts as a proteolytic factor in a variety of other biological processes, including ECM remodeling[27]. PLAU binding to its receptor (not shown), **PLAUR**, which is anchored in the fibroblast cell membrane and has a role in regulating fibroblast growth[125], promotes the cleavage of **PLG** to PL[27], a process that is also stimulated by **TGFB1**[126]. PL upregulates the expression of **COL1A1**[127] and it activates **MMP1**, **MMP2**, **MMP3** and **MMP9**[128-130]. Further, PL is inhibited by the extracellular proteinase inhibitor **SERPINA1**, which itself is degraded by **MMP1** (not shown), **MMP2**, **MMP3**, **MMP8** and **MMP9**[131]. The extracellular form of **YWHAB** (see below) is also involved in upregulating the expression of **MMP1**[132].

Since fibroblasts are responsible for the synthesis and secretion of the main ECM components through (e.g. **AHNAK**- or **TGFB1**-activated) **SMAD3** - which also plays a major role in EMT (see above) - fibroblast survival and apoptosis (and hence proper functioning) is another important landscape process. In this respect, **SMAD3** upregulates the expression of **COL1A1**, **COL3A1**[116] and **MMP9**[133], whereas it downregulates **ELN**[134] and **MMP1**[123]. Further, nuclear SPOP belongs to an E3 ubiquitin-protein ligase complex that is involved in upregulating **MMP1** expression[135].

This SPOP complex also represses the transcriptional activity of **ESR1**[136] and its activity is regulated through binding and interacting with **SPOPL**[137].

TRAIL (other name: **TNFSF10**) is a member of the tumor necrosis factor (TNF) family of extracellular cytokines that binds to its receptors, the transmembrane proteins TRAIL-R1 (other name: TNFRSF10A), TRAIL-R2 (other name: TNFRSF10B) and **TRAIL-R3** (other name: **TNFRSF10C**), which is anchored in the fibroblast cell membrane[27]. Upon binding TRAIL-R1[138] and TRAIL-R2[139], **TRAIL** triggers fibroblast apoptosis through activating **CASP3** or NFKB[140,141]. In contrast, **TRAIL-R3** competes with TRAIL-R1 and TRAIL-R2 for **TRAIL** binding and, as **TRAIL-R3** does not have a cytoplasmic 'death domain', it inhibits the TRAIL-R1/2-induced apoptotic cascades and hence protects fibroblasts against apoptosis[142]. **TGFB1** (up)regulates the expression of TRAIL-R1 and **CASP3**[143] and, as already mentioned above, NFKB is activated downstream of **TGFB1** signalling[19]. In turn, NFKB regulates the activity of **CASP3**[144,145], providing additional regulation of the TRAIL-R1/R2-apoptotic signaling cascade. In addition, **TGFB1** promotes EMT through activating miR-155[146], a microRNA that regulates inflammation and fibrosis and is involved in inhibiting **CASP3**[147] and upregulating the expression of **SMAD3**[148]. **CASP3** also cleaves (and hence regulates the activity of) **AHNAK**[149], which, as already indicated above, shuttles between the cytoplasm and nucleus[9] and stimulates the **TGFB1**-induced activation and translocation of **SMAD3** to the nucleus[10]. Further, **CASP3** (negatively) regulates the activity of **PARP1**[150,151], a nuclear protein that modulates oxidative stress-induced apoptosis in fibroblasts[152]. Moreover, **PARP1** is activated by **TRAIL**[153]. **RAD52**, a nuclear DNA repair protein that promotes the survival of fibroblasts[154], also hyperactivates **PARP1**[155]. Further, both **SMAD3**[156] and **YWHAB**[157] bind and interact with **WNK1**, a kinase that is also upregulated by **TGFB1**[158].

In addition, **COL18A1** decreases the expression of **HIF1A**[159], a transcription factor that counteracts apoptosis of fibroblasts[159]. Further, **HIF1A** binds and interacts with **ESR1**[24], **SMAD3**[160] and SPOP[161], while **TGFB1** and **HIF1A** upregulate each other's expression[162,163]. **HIF1A** is also bound and activated by **PARP1**[164], and it is involved in increasing the expression of **MMP1**[165], **MMP2**[166], **MMP9**[166], **LOX** (not shown)[167] and **PLAUR**[167]. Moreover, **NACA2** is a nuclear protein that forms a functional complex with NACA[168], a positive regulator of **COL1A1** expression[169].

Another important protein in the landscape is **vimentin (VIM)**, a cytoskeletal protein of which the expression is increased in mesenchymal cells such as fibroblasts during EMT and that regulates fibroblast function, in particular the response to mechanical stress[170]. **VIM** expression is upregulated by **ECM1**[47] and downregulated by **FBLN3**[51]. while the protein is also cleaved by **CASP3** (not shown)[171] and it is involved in increasing the production of **TGFB1** by fibroblasts[172]. **VIM** expression is also downregulated by **TBX5**[173], a nuclear transcription factor that is found in fibroblasts[174] and also downregulates the expression of both **COL1A1**[175] and **COL1A3**[175]. Moreover, **VIM** upregulates the expression of **ITGB1**[176], a membrane protein of the integrin family that downregulates **COL1A1** expression[177], is involved in regulating the activity of **COL18A1**[178] and is upregulated downstream of both **TGFB1**[158] and **PLAUR**[179]. **ITGB1** upregulates the expression of **MMP9** - which is inhibited by **FBLN5**[180] - and of **LAMC1**[181], an ECM protein that binds and is upregulated by **TGFB1**[182,183]. **ITGB1** is also bound and regulated by **EMILIN1**[184,185], an ECM proteins that is secreted by fibroblasts[186] and binds/interacts with both **ELN**[187] and **LAIR2** [188]. Further, **EMILIN1** inhibits **TGFB1** signaling[189].

As already indicated above, the **AGE**-**RAGE** complex regulates a number of downstream signaling cascades in both epithelial cells and fibroblasts. In this respect, the **AGE**-**RAGE** complex stimulates the apoptosis of fibroblasts[190] in which it regulates the activity of NFKB[21,191] and inhibits **CASP3**[192]. Further, **AGE**-**RAGE** is involved in upregulating the expression of **MMP2**[193], **MMP9**[194] - which is itself inhibited by **ECM1**[195] - and **TGFB1**[196], while it also promotes the translocation of **SMAD3** from the cytoplasm to the nucleus of fibroblasts[21].

Lastly, in fibroblasts, **MRPL35** is located in and affects the function of mitochondria through regulating the synthesis of the cytochrome C oxidase (COX) enzyme (not shown), which is part of the IVth respiratory chain complex[197] that, together with other respiratory chain complexes, may be expressed at lower levels in women with POP[198].

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