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Mapping out p38MAPK

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Abstract

In order to generate new hypotheses, sometimes a “systems” approach is needed. In this review I focus on the mitogen activated kinase p38 because it has been recently shown to play an important role in the developmental programing and senescence of normal and stressed reproductive tissues. What follows is an overview of 1) pathways of p38 activation and their involvement in basic biological processes 2) evidence that p38 is involved in the homeostasis of reproductive tissues 3) how focus on p38 can be incorporated into investigation of normal and stressed pregnancies. Existence of excellent reviews will be mentioned as well as relevant animal models.

Keywords

MAPK14 p38 pregnancy; reproduction; immunology

1. Why p38?

Efforts to delineate the molecular pathways critical to normal parturition and preterm birth have highlighted the importance of inflammation[1–6]. Further, analysis of the molecular events down-stream of senescence, oxidative stress, infection, and metabolic dysregulation in reproductive and other tissues have suggested that these events all involve the professional mediator p38 in the generation of inflammatory responses[7–11]. This and other data gives support to the development of a “p38-centric” (Fig. 1) view of cellular homeostasis that is relevant to reproduction, including normal and premature parturition.

2. Introduction to p38

Extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinases (JNK) and p38, are members of a serine/threonine kinases family with related molecules present in unicellular organisms, and thus have a long evolutionary history[12, 13]. These molecules are key in mediating cellular responses and are activated through the phosphorylation of a Thr-X-Tyr motif by upstream mitogen activated protein kinases (MAPK). While ERK pathways are typically associated with growth or proliferation signals, JNK and p38 are associated with the response to environmental and infectious/inflammatory stress. There are different

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pathways for activation of ERK, JNK, and p38, but it is likely that there is cross regulation between the pathways[14], and frequently stimuli will activate more than one pathway. The p38s comprise a group of 4 proteins p38α, p38β, p38γ, and p38δ that represent different branches on a phylogenetic tree and are each conserved among species [15]. The MAPK 14 family includes p38a in mice, rats, humans *Xenopus laevis* and zebra fish. The MAPK11 family similarly comprises p38β, while the MAPK 13 family corresponds to more loosely related p38δ. p38γ, also called ERK6 is part of the MAPK 12 family[15]. Of the p38 MAPK, p38α is most widely expressed and studied. While p38 β and δ[16], are expressed in immune cells, p38γ is not and seems to have a highly restricted expression that as yet is not completely elucidated. From here on discussion will focus on p38α and for convenience it will be referred to as p38. This molecule is activated by three upstream kinases MKK3, MKK4, and MKK6. While MKK3 and MKK6 are p38's main MAPKKs[17] specificity of the outcome of external stimuli as noted above, is determined by cell and tissue context and other associated molecules. For example, in mice, all three are involved in activation after ultra violet radiation, while only MKK3 and MKK6 are critical for TNF-a mediated activation.[18] Further upstream to the MKKs are the MEKKs 1 to 4 (also called the MAP3Ks for MAP kinase kinase kinases), MLK2/3, and ASK1 (Apoptosis signaling kinase 1), and TAK-1 (TGF-β activated protein kinase 1). Other upstream molecules will likely be delineated with further study. Another point of specificity in p38 regulation comes from the site of phosphorylation. Sites for phosphorylation pf p38 include Thr180 and Tyr182 and another level of control is exemplified by cyclophilin-dependent isomerization of p38 that modifies the chance that upstream kinases can phosphorylate p38[19].

3. UPSTREAM: how does p38 get activated?

There are several "stresses" that result in p38 activation. [20]

ER stress

Response to a stimulus includes generation of new proteins. The proper folding and transport of these proteins is monitored by the cell. The presence of excess unfolded protein generates the unfolded protein response that includes upregulation of PERK (Protein kinase (RNA)-like endoplasmic reticulum kinase), IRE1 (Inositol requiring protein 1) and ATF6 (Activating transcription factor 6), among others. This leads to an increase in XBP-1 (X-box binding protein 1) and free BiP (binding Ig protein) that can assist in chaperoning and folding the proteins. If however, such ER stress is not relived, this can lead to the interaction between ASK1 and TRAF2 and auto-phosphorylation of ASK1 which can feed into the pathway that causes MKK activation and leads to activation of p38[21]. Advanced glycation end products (AGEs), produced by the non-enzymatic glycation of macromolecules can accumulate in different tissues and mediate p38 activation through the generation of ER stress.[22] ER stress induced by infection can also elevate p38 activation.[23]

Oxidative stress

Oxidative stress leads to the activation of p38 in many tissues. For examples, direct application of cigarette smoke extract to fetal membranes leads to activation of p38.[24] In an endothelial cell line, lipid peroxidation can lead to activation of Src which in turn leads to

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the activation of p38. A first trimester human trophoblast cell line responds to hypoxia followed by reoxygenation by increasing growth arrest and DNA damage-inducible 45 alpha (Gadd45alpha) expression which in turn activates p38. Data such as this supports the growing hypothesis of the close link between inflammation and oxidative stress and further places p38 as playing a role in the crosstalk between the two processes.

Inflammatory stress

Signaling through receptors for pathogen or "Danger" associated molecular patterns, such as the Toll like receptors leads to activation of the MAP3 Kinases, including TAK-1 (TGF-b activated protein kinase 1) which then activates one of the downstream MAP2 Kinases such as MKK3/6 or MKK4. This in turn activates p38. Cytokines involved in inflammatory processes, such as IL-1 and Tumor necrosis factor-α bind to their cognate receptors and via the small GTPases (e.g. RAC1 and CDC42) also lead to p38 activation (reviewed in[25]). Specific receptors on different types of inflammatory cells mediate their functions via activation of p38, and this includes the T cell receptor. Binding of this receptor includes activation of ZAP70 and LCK, and ultimately activation of p38.[26] Viral infection can also lead to p38 activation.[27] In neutrophils, TGF-β, which with IL-6 helps to generate the TH-17 response[28], activates p38 and MKK2 and promotes chemotaxis[29].

Metabolic stress

This is a likely more broadly inclusive family of cellular stress that encompasses oxidative stress as well as other processes. Insulin, for example exerts an anti-proliferative and hypertrophic effect in an extra villous cell line, and this may be partially reversed by an inhibitor of p38,[30] suggesting a role for this molecule. Exposure of kidney cells to high salt conditions leads to p38 activation.[31] Embryonic stem cells starved of leukemia inhibitory factor die by apoptosis, and this is mediated by activated p38 and increased cleavage of caspase 3.[32]

Earlier studies have also delineated the potential role of p 38 in term trophoblast cell response to placenta derived growth factor and protection from serum withdrawal-induced apoptosis.[20] Other growth factors such as VEGF and erythropoietin all trigger p38 activation in tissue specific manner[33].

DNA damage

Ionizing radiation and other inducers of DNA double strand breaks lead immediately to histone modifications and sensors of DNA damage, including the PCNA-like complex facilitate the activation of upstream kinases such as Ataxia telangiectasia mutated (ATM), and Ataxia-telangiectasia and rad3 (ATR) [34, 35]. This in turn can trigger phosphorylation p38 and cause its nuclear translocation.[36] ATM in addition can work with NEMO (NF-κB essential modifier) to release NF-κB from IκB kinase α and β, Unprotected chromosomes induce DNA damage checkpoint cascades and has been associated with increased activation of p38[37] and may explain the association between telomere shortening and the presence of phosphorylated p38.[38, 39]

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4. DOWNSTREAM: what happens when p38 gets activated?

p38 and inflammation

Several effector pathways are induced by the activation of p38. In the so-called 'classical' p38 pathway, phosphorylated p38 in the cytosol can mediate the activation and movement of several transcription factors including AP-1 and SP-1 to the nucleus which could be followed by transcription of several inflammatory cytokines and mediators[33]. A particular example is that p38 activates mitogen- and stress-activated protein kinases, MSK1 and MSK2, which can phosphorylate the trans-activating p65 subunit of the NF-κB complex at Ser276 and thus potentiate NF-κB signaling.[40] While in the cytoplasm, activated p38 can also mediate its effects through the activation of other specific proteins including MAP-kinase activated protein kinase 2 (MAPKAPK2, MK2) and MAPKAPK5 which in turn can phosphorylate heat shock (e.g. 25/27) and other proteins in and out of the nucleus [41] Down-stream molecules of p38 activation can also stimulate the transcription factor STAT3 which can potentiate the actions of NK cells and IL-6[42].

Autophagy[43]

This is an important mechanism for homeostasis in several tissues in response to stresses such as inflammation, and evidence of dysregulation of this process has been associated with preterm birth in humans[44]. p38 can up or down-regulate autophagy[45, 46]. p38 can block autophagy through the mechanistic target of rapamycin (mTOR) pathway and pathways independent of this molecule[45]

Senescence

Senescence occurs as the result of irreversible cell cycle arrest, and is associated with DNA fragments, and stereotypic histologic changes and inflammation[40]. Activated p38 can arrest cell division by multiple pathways, including activation of p53[47] and in the so-called 'non classical' pathway p38 can move to the nucleus itself and enhance the activity of molecules such as p21 and p16 to block cell cycling[10] at both the G2M[48] and G1/S checkpoints.[47] Genomic instability evoked by senescence triggers epigenetic changes, e.g. release of HMGB1 proteins which are also potent enhancers of inflammatory responses (see feedback loops, below). Another molecule upregulated by senescence is p19ARF that, along with are thought to also behave as tumor suppressors[40]. It is possible that senescent cells sit on a precipice between cancer and death and that p38 is critically involved in the balance.

Cell death

The death of a cell can proceed along several specific molecular pathways (reviewed in[49, 50]), and p38 may be directly or indirectly involved.[51] The two major apoptotic pathways that are well documented in mammalian cells are the death receptor and the mitochondrial pathway in the death receptor pathway. The death receptor pathway involves the cysteine proteases Caspase 8, 10, and 3, and is initiated by expression of molecules like TNF. The mitochondrial pathway is an intrinsic pathway is activated in response to ionizing radiation, growth factor withdrawal, chemotherapeutics drugs, reactive oxygen and nitrogen species, and DNA damage. Such insults lead to expression of BCL-2 family members,

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mitochondrial membrane permeability, release of cytochrome c and activation of Caspases 9 and 3. Some of the pathways can be quite complex. For example, Glycogen synthase kinase 3β (GSK3β) is a constitutively active kinase that supports apoptosis through inhibition of the pro-survival transcription factors, and facilitating pro-apoptotic transcription factors such as p53[52]. In developing T cells, GSK3β phosphorylates beta-catenin and causes its degradation[53] which prevents it from supporting the transcription of pro-survival genes. However, activated p38 can phosphorylate GSK3β on Ser 389 and inactivate it, thus preserving survival.[54] Recently, inability to inactivate GSK3β has been linked to promotion of cell death via a process now called necroptosis.[49]

Feedback loops and "rogue" pathways

The "upstream/downstream" construct for p38 may be a gross oversimplification. For example, molecules such as tumor progression locus 2 (TPL-2) TPL2 participate in a circuit that is dependent on p38 activation and itself activates the MKK3/6 which in turn activates p38[55]. For another example, stressors that generate p38 activation can also result in expression of High Mobility Group B1 protein (HMGB1), but this in turn can act via internal pathways to activate p38.[56] For yet a thrid example, senescent T cells emply neither the canonical nor alternative pathways and instead cause auto phosphorylation of p38 by engaging AMPK to cause p38 recruitment to the scaffold TAB1. This process leads to loss of telomerase[57] which may lead to shortened telomeres and may itself be associated with p38 activation.

5. Tissue specific regulation of p38 and implications for normal and abnormal function

The ovary

Activation of p38 might regulate proliferation. For example, in mouse granulosa cells, exposure to FSH leads to p38-mediated de-phosphorylation of the transcription factor STAT1. This leads to decreased transcription of the cytochrome P450 1 subfamily member Cyp1b1 and altered estrogen metabolism. The result is decreased proliferation, and it is hypothesized that this assists in the maintenance of estradiol levels in the dominant follicle in vivo.[58] In addition, p38 regulates the response to prolactin in a model premature ovarian failure[59]

The cervix

Cervical mucosal epithelium responds to infection with production of TNF-α and this is in part dependent on activation of p38[60]. In human cervix, p38 activation has been associated with parturition but this is likely due to inflammatory cell traffic macrophages[61–63] and or association with tissues such as the fetal membranes overlying the cervix at term[64, 65] as this tissue expresses an increased inflammatory signature.[66]

The myometrium

This kinase is expressed in myometrial cells where it has been found to mediate may mediate oxytocin receptor signaling and downstream inflammatory responses[67]. Histamine

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also induces p38 activation in myometrial cells and this may in part explain the cross-talk between histamine and Toll like receptor triggered inflammation and further, that there is an increase in premature labor in patients with severe allergy[68] or asthma[69]. Stretch also activates the p38 pathway within myometrial cells[2, 70], and this may contribute to the inflammatory signature occurring with multiple gestation, or with the end of a singleton pregnancy.

The decidua

Overall, activation of p38 increases with gestational age in mouse decidua [38] and may be increased by labor in humans.[71] The decidua is a complex tissue[72, 73] comprised of stromal, leukocyte, glandular, and vascular elements. Each is likely to have its own regulation with regard to the mitogen activated kinases. For examples, preimplantation factor, PIF supports implantation in a process that involves decreasing p38 activation and endo-cannabinoids can induce apoptosis in decidual cells in a process that includes activation of p38, mitochondrial stress, reactive oxygen species elaboration and apoptosis.[74] Decidual stromal cell dysfunction has been implicated in early and late pregnancy loss, related to a mouse model of progesterone receptor targeted insufficiency in p53, but the role of p38 in that model is unclear[75]. In humans, p38 may mediate the inflammation related to functional progesterone withdrawal[7672].

The activation of leukocyte populations by Toll-like signalling largely involves activation of p38. For example, NK T cells are activated by Toll-like receptor, CD1, and inflammatory cytokine signaling that proceeds with activation of p38 and ERK pathways[77]. Decidual artery remodeling is an important aspect of normal pregnancy in the mouse[7879, 80] and deficient invasion of spiral arteries is thought to be an important initiator of preeclampsia. While many studies have reported the potential role of p38 activation or inhibition in systemic vascular remodelling[81], few have examined decidual vessels. Human umbilical vein endothelial cells exposed to hypoxia/reperfusion upregulate growth arrest and DNA damage-inducible 45 alpha (Gadd45α) leading to p38 activation and ultimately an increase in fms-related tyrosine kinase-1 (sFlt-1) and soluble endoglin secretion, and both Gadd45α and activated p38 are found in placentas from preeclampsia pregnancies.[82]

Preimplantation embryo and trophoblast

Several studies have delineated the expression[41] and importance[83] of p38 signaling in the development and function of the preimplantation embryo. The p38 pathway is critical for glucose metabolism[83] and differentiation[41], as well as in the generation of molecules important in implantation. Early in gestation, VEGF activates p38 and contributes to VEGF-induced EVT migration and capillary-like tube formation in human chorio-decidual trophoblast[84].

Fetal membranes

The fetal membranes represent a unique tissue that balances proliferation, renewal, senescence and death. The fetal membranes are a multilayered and multicellular tissue that includes the amnion and the chorion.[85] Over time in normal pregnancy the fetal membranes undergo senescence associated with increased expression of p38[346, 38], and express

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increased p38 with oxidative stress,[24] and in the setting of premature rupture of membranes[6, 71, 86, 87,72]. Membranes express both classical and alternative p38 pathway molecules, but cell type specificity, and the exact up and downstream activators and effectors are not known.

6. The future of p38 in reproductive science

Animal models of reproductive outcome

There exist several models of reproductive outcome.[88–90] With regard to the role of p38, animal models, particularly mice offer the opportunity to examine both the kinetics and the specific molecular pathways by which activation of this molecule occurs and causes downstream effect. Studies in normal mice mice[38] suggest that progressive increase in activated p38 occurs in the decidua, placenta and fetal membranes. However, the relevant pathways and cells are unclear and will have to be examined in future studies and correlated with findings in humans. [71, 91, 92,49] Although some of the stressors leading to poor pregnancy outcome humans can be modeled in mice, the specific p38-involved pathways have yet to be fully explored.

Biomarkers of p38 activation

Peripheral blood cytokines and molecules such as sFlt have been used to predict abnormal pregnancy and may be down stream of p38 activation[93]. As activation of p38 is a pivotal event in many processes indicative of pregnancy stress or disregulation, it would be useful to have early indicators of p38 activation. In vitro, exosomes from aminon epithelial cells contain activated p38 and uptake into the cytoplasm of other cells activates inflammatory pathways.[94] Vesicles, including exosomes[95] eminate from several tissues of the reproductive tract and can be found in maternal blood. This raises the interesting idea that exosomes be used to diagnose early placental p38 activation.

Inhibitors and activators of p38 at the bedside

The clinical importance of modifiers of p38 activity and an approach to development of these drugs has been recently reviewed.[96] Focus has been on inhibition of the catalytic activity of p38 is through competitive or non-competitive binding of ATP[97]. Many inhibitors of p38 are being considered, including SB203580 (a competitive binder in the ATP pocket or p38), and BIRB 796[97] in diseases related to premature ageing (e.g. Werner Syndrome[97]) and autoimmunity. Focus on how to target drug activity and limit side effects continues. Further, there exists a pipeline to develop ways to modulate molecules down stream of p38 activation[81, 96] in specific cell types[98] order to increase specificity. Relevant clinical trials focusing on reproductive outcome need to be developed. Agents, such as statins[99] are being considered for improvement of reproductive outcome, and have an indirect action on the p38 pathway through decreasing upstream stressors such as oxidative stress[100], but further understanding of these agents is also needed.

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7. Summary

p38 is part of an evolutionarily conserved family of molecules that plays a pivotal role in homeostasis in the reproductive tract. Certain cell types, including immune cells, employ canonical, alternative or “rogue” p38 pathways. Consideration p38’s roll in cell-cell interaction in the reproductive tract and beyond is crucial. Focus on the molecular stresses leading to increased expression of activated p38 as well as down-stream effector pathways will lead to greater understanding of normal and abnormal reproduction.

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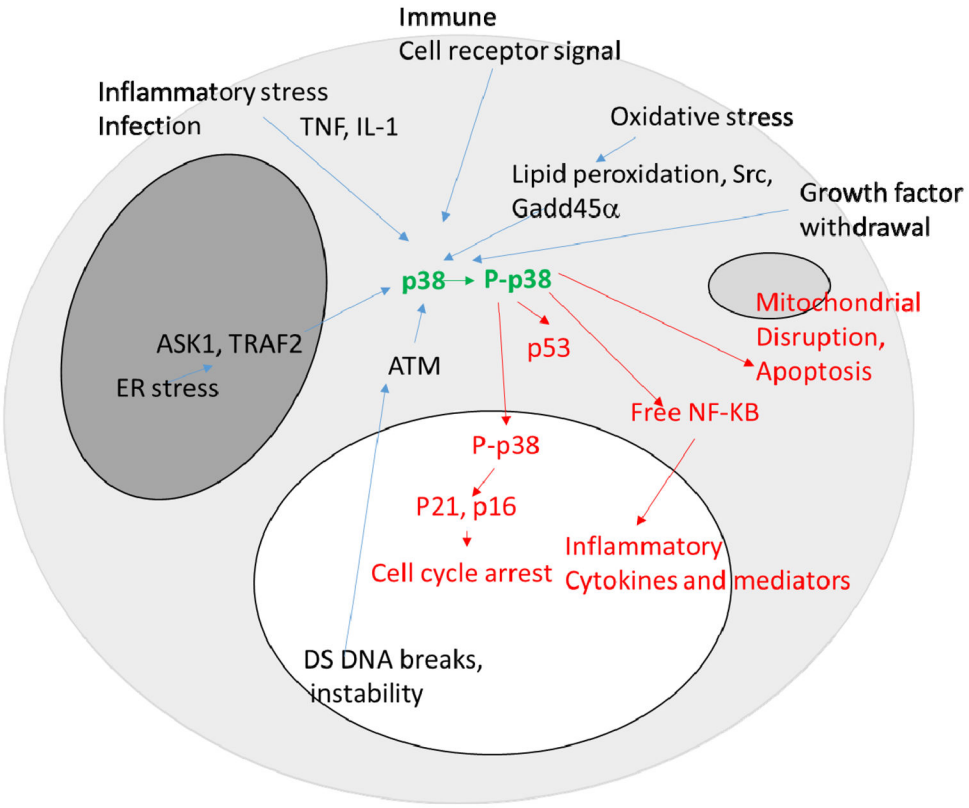

Fig. 1. A p38-centric view of cellular homeostasis

A stylized cell with dark grey endoplasmic reticulum, light grey mitochondria and a while nucleus is shown. A sampling of factors leading to increased presence of activated (phosphorylated, P-p38) p38 are shown with blue arrows/black writing, while events downstream of p38 activation (green) are shown with red arrows and writing. ASK-1 (Apoptosis signaling kinase 1), TRAF2 (TNF receptor-associated factor 2), GADD45α (Growth arrest and DNA-damage-inducible protein GADD45 alpha), TNF (Tumor necrosis factor), IL-1 (Interleukin 1), NF-κb (nuclear factor kappa B) are all shown as representative molecules in the p38 ‘universe’.