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P38 kinase signalling in diverse diseases: variety and adaptability

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ABSTRACT
The mitogen-activated protein kinase (MAPK) family of enzymes regulates a wide range of cellular behaviours in response to environmental stimuli. p38 MAPKs are key signalling molecules that regulate pro-inflammatory cytokines and cellular responses to environmental stresses. It makes sense that p38 might be effective for treating a range of ailments, including cancer, immunological conditions, and inflammation, given that p38 regulates so many distinct processes. In addition, increasing evidence points to the p38 MAPK signalling cascade's involvement in biological processes other than inflammation, such as cell proliferation, differentiation, apoptosis, and invasion, suggesting that the p38 MAPK could be used as a potential therapeutic target for the management of both inflammatory diseases and cancer.

Keywords -MAPK, P38, LPS, GPCR, CSBP2, CSPB1, EXIP12, TNF-α, MAP2K, MAP3K, MKK3, MKK6, TAB-1, TAK1, ZAP70, DUSP1, RANKL, MMP-2, MMP-9, MMP-13, COPD, PDL-1, BAL, Cancer,Asthma, Smac mimetics, Lewy body.

I. INTRODUCTION/BACKGROUND

The mitogen-activated protein kinase (MAPK) p38 is sometimes referred to as the stress-activated MAPK due to its sensitivity to cytokines and cellular stress. However, P38 also serves other physiological functions. The terminal kinase in numerous signalling cascades is P38, a MAPK that is triggered by two phosphorylation's. Effective stress management is essential for cell and organism survival because, despite the fact that most cells experience different types of stress throughout their lifetime, in both pathological and homeostatic settings, stress may be harmful. The signalling networks that cell use to react to stress depend on P38 kinases. Many signalling networks are essential to cells. All eukaryotes have proline-directed serine/threonine kinases, commonly known as p38 kinases, which belong to the yeast-like mitogen-activated protein kinase (MAPK) family and share structural and regulatory similarities with yeast. Many studies have now shown a link between p38 kinase and cellular responses to most stimuli, including wounds from both internal and external sources, healthy activities, and diseases including infections and cancer. Yet causing stress from such cell differentiation (1-6) The extracellular environment is always changing, and MAPK serves as a marker of these changes. This causes cellular responses that enable cells to adapt to these changing normal and pathological situations. The target genes of transcription factors, cytokines, and their surface receptors are activated by p38 MAPKS, acting as a "kill switch" to enable a complete cellular response. Hence, these proteins are seen as potential therapeutic targets to fight the ineffective inflammatory response.

Family members of the p38 kinase

The first mammalian p38 protein is a 38 Kdaprotein that is induced by lipopolysaccharide (LPS) (7) to become tyrosine phosphorylated, according to four independent experiments. CSBP2, a protein kinase that is triggered by arsenic acid, heat shock, or osmotic stress, and RK (8), an anti-inflammatory drug with properties similar to those of SB203580's pyridinylimidazole. Remarks on (9), and saccharomyces cerevisiae. A MAPK called HOG1 has been shown to imitate the proteins p38, RK, p40, and CSBP2 and help in the defence against osmotic stress. The designations p38β, p38γ, and p38δ were later given to other proteins that had a lot of similarities with the protein known as p38α. CSPB1 (10), EXIP12,MXI2 (11-12) and p38 are examples of spliced variations of p38α that have been proven to function and contribute to cellular pathology. Mammalian P38 kinases are 60% homologous in amino acid sequences and p38αis 75% similar to p38β and p38γ being 75% similar to p38δ. While the p38kinases are structurally identical, their downstream targets and susceptibilities to pharmacological inhibitors like the frequently used SB203580 differ (13-14). A biological enzyme

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having several roles in tissue growth and homeostasis is p38 kinase. There are clear functional differences among family members. Due to its critical role in placental morphogenesis, P38α is the only p38 kinase required for mouse embryonic development (15-17). Yet, when p38α is present, p38β overlaps significantly (18-19). This can be because p38α is expressed more often in most cell types, but it might also be because of the specific roles that p38α might perform. This restores the mice's lack of p38β participation Yet, studies utilizing cell culture have identified certain tasks that p38β may excel at. Generally speaking, p38α and p38β work in concert to develop the heart (20-21), establish sex (22), prevent mitotic entrance (23), and activate regulatory T cells (24). While neither p38γ nor p38δ has been genetically shown to perform p38α function . p38γ and p38δ often play comparable functions, such as in tissue regeneration and immune responses (25). It's noteworthy to note that decreasing p38α might increase p38γ activation or p38δ activation(26-28). The upstream regulatory mechanisms vary from other family members. More understanding of the individual behaviours and functional relationships of the four p38 kinases is required in order to completely appreciate the biological function of this signalling pathway.

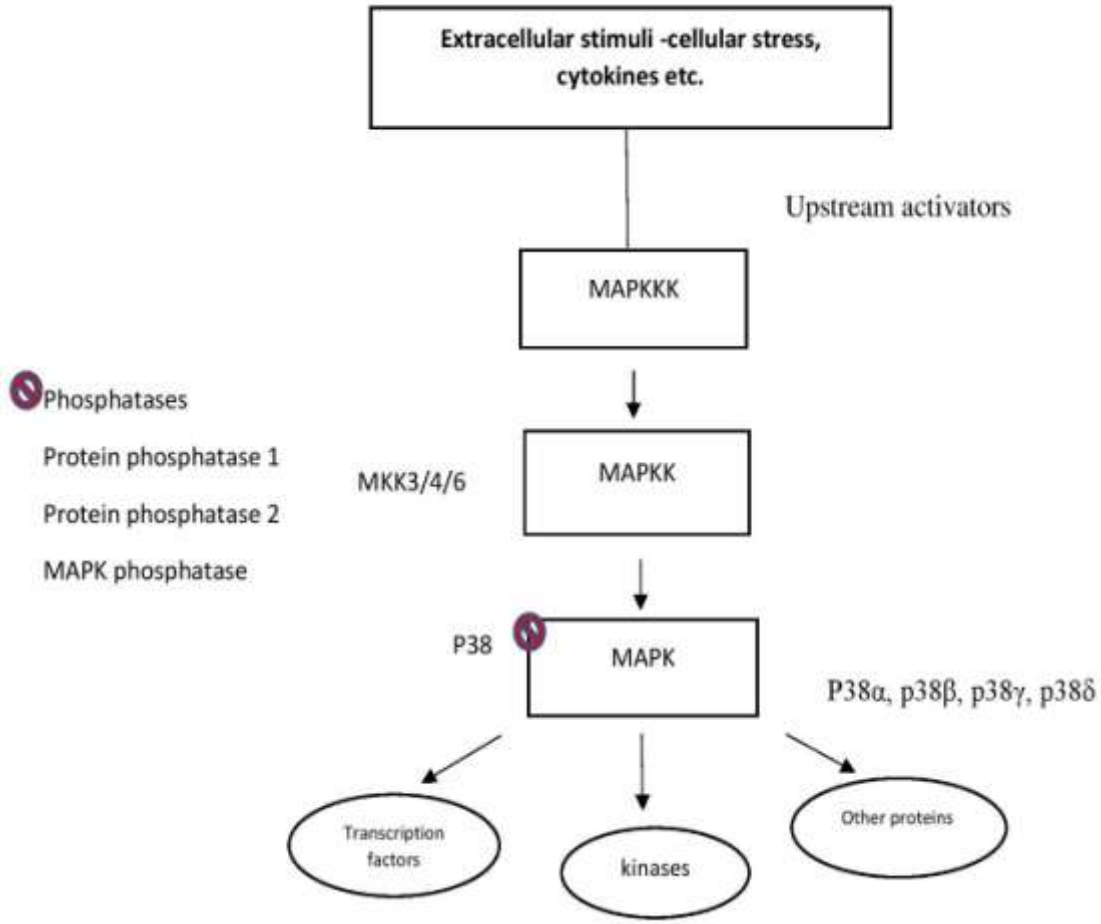

Figure:1 Schematic representation of the p38 mitogen-activated protein kinase signalling pathway.

P38 kinase-mediated signalling

The activity of p38 kinases may be controlled by feedback loops, activated by specific kinases that integrate many inputs, inactivated by various phosphatases, and impacted by a variety of translational routes that affect various signalling pathway components.

Activation of the p38 MAPK signalling pathway and its operation

A lot of research has accumulated on the activation of p38 MAPK in inflammatory responses since the discovery of mammalian p38 MAPK during inflammation. Proinflammatory cytokines that activate p38 MAPK include interleukin and TNF- [29–30]. G-protein-coupled receptors

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(GPCRS), cytokine receptors, toll-like receptors, growth factor receptors, and receptors connected to environmental stress, such as heat shock. Radiation and UV light are reportedly additional signalling events that activate the p38 MAPK pathway [31,32,33]. It should be emphasized that the level of p38 MAPK activation depends on the type of cell [34,35]. There is evidence that some p38 MAPK isoforms are selectively activated by upstream kinases [36–39]. The upstream MAPK kinase (MKK) is involved in the activation of p38 MAPK [40, 41]. Whereas MKK3, which is 80% homologous to MKK6, activates all four of her p38 isoforms, MKK3 promotes p38α, p38γ, and p38δ. According to various studies [41–45], MKK6 is the main activator of p38α MAPK. MKK4 also phosphorylates p38α and p38δ in certain cells in response to particular stimuli [36]. There are several signalling channels that link the MKK/p38 network. In human 293T kidney cells, MKK7 activates p38δ [37]. It has been discovered that RAC and Cdc42 may act as regulators of the p38 MAPK signalling pathway. IL-1 does not increase p38 MAPK activity when RAC and Cdc42 are dominant-negative constructs, but p38 MAPK is activated when these two proteins are co expressed. [46-47]. Our laboratory's studies have shown that mutant H-Ras essentially activates p38 MAPK in human mammary epithelial cells [48]. The p38mapk signalling pathway involves both small and giant G proteins, including GPCRSand regulatory G protein signalling proteins (RGS) [49–50]. The MAPKAP kinases MK2, MK3, and p38 regulatory/activated kinase (PRAK), which it preferentially phosphorylates, are downstream substrates of p38-MAPK. Comparatively to MK3- and PRAK-deficient animals, MK2-deficient mice produced much fewer cytokines, such as TNF-a and IL-6, and they were less resistant to endotoxic shock [51–52]. P38 MAPK and MK2 were shown to be pre-assembled in cell nuclei [53]. When p38 is phosphorylated, MAPK MK-2's nuclear export signal is moved to the carboxyl-terminal domain, allowing it to travel between the cytoplasm and nucleus [54]. The fact that MK2 has to be phosphorylated in order for p38 MAPK and MK2 to exit the nucleus is proof that this step is necessary for the translocation mechanism [53]. MK3, a protein kinase that interacts with p38α, has also been shown to be a substrate for p38α [55]. P38α and p38β may activate the stress-induced protein PRAK [56].

Activation mechanism

The simultaneous phosphorylation of MAP2K, followed by the phosphorylation of MAP3K, activates P38 kinase. The activation of p38 kinase has been demonstrated to include up to 10 MAP3Ks, even if some of them may also activate other MAPKS, most notably JNK. The diversity of the upstream components of the p38 kinase cascade allows the signalling pathway to adapt to a range of stimuli and provide flexibility in response. Several signals are used to activate a number of MAP3Ks. MKK3 and MKK6 of MAP2K, which share 80% of their amino acid sequence and are highly selective for p38 kinase, or MKK4, which typically activates JNK but may also activate p38α, are phosphorylated by MAP3K. Oxidized (17). Depending on the cell type and external stimuli, MAP2K is involved in p38 kinase activation in a variety of ways. For the kinase to work properly, MAP2K must phosphorylate the Thr and Tyr residues (Thr180 and Tyr182) in the p38α activation loop. The common phosphorylation cascade that occurs in the majority of MAPKSis a typical activation mechanism for them. Together with the phosphorylation cascade based on MAP2K, there are two other pathways that might activate p38. One is in charge of attaching to transforming growth factor-activated kinase 1, while the other is in charge of interacting with TAB1, which results in p38α autophosphorylation. (56). This mechanism in cardiomyocytes during myocardial ischemia has been well studied (57-59). Moreover, dermatitis (60), endothelial inflammation brought on by G protein-coupled receptor agonist (GPCR), white adipose tissue darkening produced by triiodothyronine (61), T cell aging (62), and is also connected. The usual technique may be used by TAB1 to bind MAP3K TAK1 and activate p38. The only T cells in her that seem to engage her third non-canonical pathway of p38α activation are those that have been activated by the T cell receptor. This has ZAP70, which phosphorylates Tyr323 to produce p38α and p38β autophosphorylation (64). Tyr323-induced autophosphorylation of p38α occurs just at Thr180 as opposed to the conventional method in which p38α is dual phosphorylated by MAP2K and this monophosphorylated p38 α alters substrate selectivity in vitro. (65). Different activation methods provide more control over pathway-modifying activity, improved selectivity in locating relevant targets, and more control over responses in a variety of cell types and environments.

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Signal termination

As over activating p38 often has detrimental effects on the cell, signal termination systems are essential for maintaining homeostasis. The p38 activation loop may be phosphorylated by a variety of phosphatases, including as serine/threonine phosphatases, tyrosine phosphatases, and dual-specificity DUSP/MKP family phosphatases. The possibility that p38 signalling may activate DUSP1, resulting in a negative feedback loop that might produce asynchronous oscillations and cell-to-cell variability in p38 activity, is fascinating to note. It has been shown that both stress-induced cell death and the production of pro-inflammatory genes rely on this. (66-68). The restriction of MKK6 (69), phosphorylation of TAB1 (which may affect both non-canonical and TAK1-mediated canonical activation (70), and phosphorylation of ZAP70 (which may affect the Association of ZAP70 with shortens the TCR and reduces p38α activation in T cells) (71) are additional negative regulatory loops that p38α may activate. The strength of the p38α signal may also be affected by negative feedback loops. The p38 activation loop must be dephosphorylated in order to downregulate the coupling pathway.

P38 in various diseases

Increasing evidence points to the p38 MAPK signalling pathway as a cause of cancer and inflammatory diseases. To investigate the role of p38 MAPKSin a variety of illnesses and to take their inhibitors into account as potential treatment strategies. Monocytes, synovial cells, and cultured alveolar macrophages from guinea pigs all express proinflammatory cytokines such TNF-, IL-1, IL-2, IL-6, IL-7, and IL-8. The proliferation and differentiation of immune system cells are also controlled by the p38mapk signalling pathway. It operates, displays, and contains endothelial cells. GM-CSF, CSF, EPO, and CD40-stimulated cell proliferation and/or differentiation are mediated by the p38 MAPK. MMP-2, MMP-9, and MMP-13 are only a few MMPSlinked to inflammation whose expression is regulated by the p38 MAPK pathway [72,75]. Moreover, p38-MAPK regulates the production of RANKL to prevent the development of osteoclasts and prevent bone resorption. (76) Enhanced p38 signalling may not always be the underlying cause of a given sickness, even while elevated p38 phosphorylation is often detected in disease conditions. P38 activation in this case could not even be a consequence, but rather a pathogenesis-related outcome. Yet, when a disease worsens, p38 may take on new functions that encourage pathogenesis while lowering pathway activity. Can. Yet, aberrant p38 activation often has unknown reasons.

The role of p38 in asthma

Wheezing, chest tightness, dyspnoea, and prolonged coughing are some of the signs of asthma [77]. Asthma is an allergic reaction that causes airway inflammation and irritation. Type 2 (Th2) mast cells, B cells, eosinophils, and helper T cells all contribute to the development and maintenance of allergy-related asthma. Th2 cells emit pleiotropic cytokines including IL-4, IL-5, and IL-13 when they become activated, which regulates B cell proliferation, IGE production, airway eosinophilia, mucus secretion, and ultimately results in airway hyperresponsiveness (AHR) (78). The p38-MAPK signalling pathway, which is involved in the generation of inflammatory cytokines and environmental stress, may be related to autoimmune diseases, asthma, and both [79]. A variety of in vitro and in vivo models of inflammation, as well as their use in the treatment or management of illnesses like asthma, have shown the efficacy of p38 MAPK inhibitors. It has been shown that SB203580 reduces TNF-a and IL-1b production in rat bronchoalveolar lavage (BAL) fluid [80,81]. Another p38 MAPK inhibitor, SB239063, reduced the levels of IL-8, IL-6, MMP-9, and neutrophil infiltration in the rat BAL fluid after endotoxin inhalation. (82)

Role of p38 in COPD

Chronic obstructive pulmonary disease (COPD) is characterized by a growing obstruction of airways and an abnormal inflammatory response of the lungs to potentially harmful substances or gases. Current therapies are unable to stop the progression of COPD or the inflammation of the small airways and lung tissue. Nowadays, clinical research is being undertaken on a variety of cutting-edge anti-inflammatory drugs. One of the several complex enzymatic cascades that contribute to COPD inflammation is the p38-MAPK pathway. It is triggered by cellular stress and regulates the release of pro-inflammatory cytokines including IL-8, TNF-, and MMPS. Patients with COPD have selectively higher levels of certain p38 isoforms in their alveolar macrophages. This implies that with the onset of COPD, the p38 MAPK signalling pathway is active. The pharmaceutical target p38 MAPK for the treatment of COPD is a promising

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one, according to these data. A multitude of COPD symptoms, including mucus overproduction and secretion, inflammation, cytokine expression, apoptosis, T-cell activation, matrix metalloproteinase production, and fibrosis, have been associated to COPD activation, constitutive, according to recent research by Connecting. Small-molecule p38 MAPK inhibitors were used to further validate these results [84]. A few examples of small molecule p38 MAPK inhibitors with anti-inflammatory properties include SB-203580, SB-239063, and RWJ-67657.

Role of p38 in kidney diseases

Immunostaining of human biopsy specimens showed considerably more p-p38+ cells in the glomeruli and tubules as well as interstitial p-p38+ cells in proliferative glomerulonephritis. (85). Myofibroblasts that were positive for muscle actin (SMA+), invader neutrophils and macrophages, and kidney-specific cells all had p38 activation. Rice field. The number of p-p38+ glomerular cells correlate with crescent development, segmental proliferative and necrotic lesions, and macrophage accumulation. The level of interstitial inflammation is also correlated with interstitial p38 activation (86-87). Moreover, the quantity of p-p38+ podocytes, tubules, and interstitial cells as well as the number of p-p38+ glomeruli, tubules, and interstitial cells were associated with proteinuria and renal failure. With respect to the severity of tubulointerstitial lesions, the frequency of p-p38+ tubulointerstitial cells correlates, and diabetic nephropathy in both humans and animals is associated with a significant rise in p-p38 activation. (88). These studies suggest that p38 activation may be a substantial pathogenic factor in human renal disease. Research has also been done on the connection between JNK signalling activity and human kidney illness. Many types of glomerulonephritis, hypertension, and diabetic nephropathy show drastically enhanced JNK activity based on immunostaining of phosphorylated-c-Jun, a distinct hallmark of JNK signalling. (89). Glomerular structures JNK signalling has been connected to the pathophysiology of numerous types of human renal disease, and p-c-Jun staining in the tubulointerstitium correlates with interstitial fibrosis and renal failure. In actuality, the degree of glomerulosclerosis is correlated with the number of glomerular p-c-Jun+ cells.

P38 and cardiovascular conditions

The modulation of cardiomyocyte fibrosis, hypertrophy, and death by p38α may have an effect on heart failure (90). The fact that heart diseases like atherosclerosis and myocardial ischemia (90-91) often coincide with activation of this system supports the therapeutic use of p38α inhibitors. P38 inhibitors were ineffective in reducing the incidence of major ischemic cardiovascular events, while being well tolerated in phase III clinical trials and reducing certain inflammatory components (92-93). A different plan of action, B, has been suggested. Targeting of TAB1-induced p38α activation coupled to MK2 inhibition (94) or cardiomyocyte death during ischemia-reperfusion (95). Yet, given the many preclinical studies highlighting the benefits of reducing p38 signalling, p38 signalling inhibition is supported by the associated advantages.

Role of p38 in rheumatoid arthritis

A persistent systemic inflammatory condition called rheumatoid arthritis may cause damage to many tissues and organs. The result is swelling in the internal organs and/or the lining of the joints [96]. In preclinical studies, small-molecule inhibitors of the RA-related p38 MAPK signalling pathway have shown therapeutic potential [97, 98]. SB203580 and SB220025 were successful in treating arthritis brought on by collagen in mouse models. These components slowed the spread of the sickness [99,100]. When used as an adjuvant, the pyridinylimidazole SB242235 reduces TNF- and has anti-arthritic properties [101]. R-130823 prevented mice from developing arthritis caused on by collagen by reducing hind paw oedema [102].

P38 in inflammatory bowel syndrome

Many inflammatory disorders that affect the colon and small intestine together go under the umbrella term "inflammatory bowel disease." In inflammatory bowel disease, P38. It has been shown that IL-23 is overexpressed in tissues from animal models of inflammatory bowel disease [103]. In terms of cellular and pro-inflammatory cytokine production, intestinal inflammation was significantly reduced by IL-23 knockdown [103]. Inflammatory bowel illness may start because of the NF-kb and MAPK cascade pathways, it has been shown. A recent study found that SB203580 reduced proinflammatory cytokine mRNAlevels and improved histological changes in animals with ulcerative colitis caused by dextran sodium

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sulphate (DSS) [104]. The Rip-like caspase-interacting apoptosis-regulating protein kinase (RICK), which is highly activated by the experimental onset of colitis, is an essential part of the signalling cascade that promotes NF-kb. Treatment with SB203580 significantly lowers this activation [104].

P38 in Neuronal regulation and roles in neurodegenerative diseases

Understanding neuronal excitability (105), synaptic plasticity (106), or myelination (107-109)processes specific to certain neurons or glial cellsis essential for comprehending brain physiology (110). P38α is related to neuropathy as well. Examples include the stimulation of microglial p38 and the generation of pro-inflammatory cytokines, both of which are associated with neuropathic pain and result in neuronal hyperactivity and pain hypersensitivity. The therapeutic potential of blocking p38α in the transmission of pain is being investigated in clinical studies (111). Nevertheless, no drugs have yet been approved, thus interest seems to be waning. Nonetheless, the therapeutic usage of p38α inhibitors may be used to treat neurodegenerative diseases. One of the early signs of Alzheimer's disease is the presence of phosphorylated p38α (112-114). The DUSP1 phosphatase is often downregulated in Alzheimer's patients' brains, and overexpressing the enzyme in mouse models promotes cognitive decline (115). As growing neuroinflammation, amyloid plaques and hyperphosphorylated tau protein accumulate in the complex disease of Alzheimer's dementia. P38α is one of these processes. Moreover, p38α suppression reduced neuroinflammation in a mouse model of Alzheimer's disease (116), which was associated with improved spatial memory. Preclinical studies in several animal models have raised the possibility that p38α is a potential therapeutic target for Alzheimer's disease (117-118), ecological culture His MK2-deficient rats treated with neurotoxins had reduced neuroinflammation and less dopaminergic neuron loss, which provided more evidence for the potential benefit of inhibiting p38 signalling in Parkinson's disease. (119-120). Amyotrophic Lateral Sclerosis (ALS), which is brought on by motor neuron degeneration that eventually leads in cell death, manifests later than Alzheimer's disease and Parkinson's disease (121). In ALS mouse models and human patients, her p38α protein has been shown to activate both motor neurons and microglia (122). Inhibition of P38α in mice or retrograde axonal cultures of human motor neurons improves ALS-related abnormalities, including loss of survival (123-125) Moreover, p38α inhibition normalizes behavioural and physiological deficits in mouse models of autism spectrum disorders, indicating that this medication is efficient in treating this condition. The therapeutic potential of p38α, like that of ALS and Parkinson's disease, has not yet been determined.

P38 in Cancer

While p38 MAPK has been extensively studied for its role in inflammation, a growing body of research indicates that p38 MAPK also has a role in a variety of cellular responses related to cancer. Results that have been incongruent in many systems and circumstances have hampered our understanding of how p38 MAPK functions in cancer. Depending on the cellular environment and level of activation, the majority of p38 MAPK responses either protect cells from stress and stimulation or damage them. It has been shown that p38α is effective in stopping oncogene-induced malignant cell transformation in normal epithelial cells. This transformation may be brought on by a reduction in cell proliferation, an increase in cell death, or an increase in cell differentiation (126-127). It was initially identified as a way to slow the development of Subsequent studies in animal models of skin, liver, lung, and colon cancer (128-129) revealed that p38α is genetically downregulated, which promotes the growth of tumours (130). These results suggest that p38α may prevent tumour growth both in vivo and in vitro. Findings from several experimental scenarios suggest that malignant cells often choose this path to promote tumour formation. Because of this, studies in murine models of colon, breast, and lung cancer reveal that the p38α protein may activate a variety of pathways in cancer cells to promote the development of primary tumours in vivo. These techniques include altering DNA repair, creating extracellular chemicals that promote the growth of cancer cells, and altering internal signalling pathways that regulate cell survival and proliferation (131-132). Moreover, p38 may promote the development of breast, ovarian, and melanoma cells by concentrating on many proteins that regulate cell motility, extravasation, and epithelial-mesenchymal junctions. (133-137). It has been shown to restrict the early spread of HER2-positive (also known as ERBB2) breast cancer cells and colon cancer cells' potential to fill the lungs of

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liver metastases, indicating that its effect on cancer cell dissemination is context-dependent (138). Depends. Subordination (139). (139). The p38-MSK1 axis also regulates the diffuse ER+ breast cancer cells latency (140). The environment that cancer cells encounter during the first stages of tumour formation and metastasis may have an impact on p38's regulatory role. Recently, there has been more focus on the function of p38α in interactions between cancer and non-cancer cells in the tumour stroma. Many ways of her P38α signalling in fibroblasts have the potential to promote the growth of tumours. Cancer cell metabolism can be induced by cytokines that mobilize glycogen inside cancer cells and release glucose (141), extracellular matrix remodelling by producing hyaluronic acid to create the tumour niche (142), cytokines that encourage neutrophil infiltration into the lung by chemokine expression (143), or any combination of these. In addition, immune cells including macrophages and dendritic cells have been shown to promote inflammation and the p38α pathway (144), which have both been associated to the emergence of colon cancer in mouse models (145). Additionally, non-canonical p38α activation in T cells promotes inflammation that supports pancreatic ductal cancer (146). Cancer cells also produce cytokines and chemokines that attract myeloid cells with tumour-promoting characteristics to the tumour niche in dependence on p38229, and it has been shown that the p38-MK2 axis is responsible for the overexpression of the T-cell inhibitory protein PDL1 in cancer cells (147), which favours immunosuppressive signalling. According to the chemotherapy medication and tumour model, p38 activity has been connected to the response to chemotherapy and has been implicated in the development and metastasis of malignancies. Oxaliplatin (148) or the nucleoside analogues gemcitabine and cytarabine, as well as other chemotherapy agents like cisplatin or 5-fluorouracil (149), often result in reduced cell death when p38α is inhibited. In vivo models are being utilized to better anticipate how patients will react to p38α inhibitors due to the diversity in p38α activity reported in known cancer cell lines, the significance of p38α in tumour stroma, and the involvement of stromal cells to response to crucial treatment. Studies using p38α inhibitors and in vivo chemotherapy in this region have shown encouraging outcomes. Pharmacological inhibition of p38α lowers resistance to the multikinase inhibitor sorafenib (150) in a liver cancer model and increases the cytotoxic effects of taxanes in mouse and human breast cancer models when combined with cisplatin (151). Moreover, the effectiveness of these targeted medications is increased by checkpoint kinase 1 (CHK1) inhibitors in KRAS or BRAF mutant tumours, or by Smac mimetics in leukaemia (152) or Smac inhibitors in leukaemia (153). Stimulates interest in alternatives to the present pairings. Cancer treatment in example, blocking the p38-MK2 signalling pathway may shield mice from the bone loss brought on by chemotherapy(154).

P38as a novel therapeutic

Chronic illnesses including autoimmune and neurological disorders demand long-term therapy since p38α signalling may govern a range of activities, which might have negative side effects or indicate the need for blocking or become ineffective. As a consequence, when administered immediately in conjunction with other medications, p38α inhibitors may be more successful in treating certain disorders, such as cancer (155-156). New tactics are being developed to block p38α signalling. Agents that target p38α depletion (157) or have the potential to target p38α to tissues (158) should be researched in order to maximize effectiveness and reduce negative effects of systemic delivery. Moreover, it has been shown in a mouse model that lowering inflammation prevents p38α nuclear translocation, which exclusively influences testicular p38α activity. It would also be intriguing to investigate the potential for creating medications that replicate the effects of p38α phosphorylation on substrates of tumour suppressors (159-160).

II. CONCLUSION:

Key cellular pathways connected to inflammation and cancer involve the p38 MAPK in a significant way. The p38 MAPK pathway's characteristics with regard to activation and function are outlined in this review. We go through the special qualities of p38 MAPK and emphasise its role in inflammatory conditions and cancer.

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