Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 2020, *19*, 206-221

REVIEW ARTICLE

The Trinity of Matrix Metalloproteinases, Inflammation, and Cancer: A Literature Review of Recent Updates

Erva Ozkan[1] and Filiz Bakar-Ates[1,*]

[1]*Department of Biochemistry, Faculty of Pharmacy, Ankara University, Ankara, Turkey*

ARTICLE HISTORY

Received: August 27, 2019
Revised: October 02, 2019
Accepted: October 10, 2019

DOI:
10.2174/1871523018666191023141807

Abstract: The critical link between cancer and inflammation has been known for many years. This complex network was further complexed by revealing the association of the matrix metalloproteinase family members with inflammatory cytokines, which were previously known to be responsible for the development of metastasis. This article summarizes the current studies which evaluate the relationship between cancer and inflammatory microenvironment as well as the roles of MMPs on invasion and metastasis together.

Keywords: Cancer, cytokine, inflammation, matrix metalloproteinase, TIMP, inhibitors.

1. INTRODUCTION

Matrix metalloproteinases (MMPs) are a zinc-dependent endopeptidase family mainly responsible for tissue remodeling in various physiological and pathological processes [1]. They play a significant role in degrading extracellular matrix (ECM) through their proteolytic functions which is crucial in providing a convenient environment for cell growth and morphogenesis [2]. Up to date, 24 members of MMPs have been identified in humans [3]. All of them are expressed in their latent forms and require subsequent activation to perform their proteolytic activity against ECM. They are regulated mainly by tissue inhibitor of metalloproteinases (TIMP) [4, 5].

Altered regulation of MMPs can result in various diseases such as cancer, arthritis, nephritis, atherosclerosis, and ulcers [6, 7]. A large body of literature confirmed that in cancer, MMPs contribute to many tumorigenic processes such as angiogenesis, proliferation, metastasis, and invasion [8]. For instance, the MMP-2 expression level was measured in epithelial ovarian cancer cells (EOC) and a direct relation was found between MMP-2 levels and the degree of invasiveness along with metastasis of the cells [9]. Similar results were found in another study performed on the EOC where the expression level of MMP-2 and MMP-14 were investigated. The results showed that both MMPs were highly expressed in these cells compared to healthy tissues [10]. MMP-1 is also observed to be up-regulated in a wide range of advanced cancers where the majority of the cases revealed a significant negative correlation between its expression and patient survival [11]. On the other hand, MMP-12 has been observed to be overexpressed in non-small cell lung cancer exhibiting a positive correlation with metastasis [12] as well as in esophageal squamous cell carcinoma with lymph node metastasis [13]. Several studies demonstrated MMP-9 overexpression in many cancer types including breast cancer, lung cancer [14], osteosarcoma [15], colorectal cancer [16], and cervical cancer [17]. Furthermore, MMP-7 expression has been positively correlated with the aggressiveness of oral and cutaneous squamous cell carcinomas [18].

*Address correspondence to this author at the Department of Biochemistry, Faculty of Pharmacy, Ankara University, Ankara, Turkey; Tel: 0312 2033055; Fax: 0312 2131081;
E-mail: fbakar@ankara.edu.tr

1875-614X/20 $65.00+.00

Numerous compounds targeting MMPs, both natural and synthetic, have been tried in cancer studies in an attempt to inhibit tumour growth and metastasis. Those that were effective in suppressing the expression of MMPs also prevented cancer cells from growing and proliferating which shows the undeniable significance of these enzymes in cancer progression [19].

The aim of this review is to discuss the role of inflammation and its mediators in cancer microenvironment as well as their contribution to invasion and metastasis through MMP-related pathways.

1.1. The Link Between Inflammation and Cancer

For decades, researchers have put an enormous effort into understanding the mechanism of cancer growth and progression. Over the years it has become evident that cancer is not all about a pile of overly proliferated cells but rather an entire system involving blood vessels, immune cells, inflammatory mediators, and many other factors that help cells constantly grow and spread. Hence it is crucial to explore and decipher the roles of a tumour microenvironment along with its components and how they contribute to cancer progression, in order to come up with an effective approach in therapy. In this section, a number of inflammatory mediators and their functions in cancer will be discussed.

Cancer and inflammation were linked in 1863 by Rudolf Virchow for the first time, after finding immune cells in tumours. But it was not considered to be an indicator of cancer until after it became evident that inflammation causes genetic instability and downregulation of DNA repair pathways [20].

Inflammation is an immune response of organisms to cellular stress, tissue injury, and infections. It helps restore tissue functions through several repair mechanisms [21]. A large number of factors are involved in this process and it includes various crosstalks between immune and non-immune cells like endothelial cells, epithelial cells, and fibroblasts. Contrary to healthy tissues, cancerous cells develop a mechanism that constantly triggers inflammatory reactions leading to chronic inflammation [22]. Because, as tumour cells grow bigger and proliferate rapidly, they start demanding urgent oxygen and nutrition supply for their survival. As a consequence, they release various chemical signals that draw immune cells such as macrophages and granulocytes into the tumour site. Following this infiltration, molecules called cytokines are produced by the immune cells which trigger angiogenesis to provide necessary oxygen and nutritions. On the other hand, several other chemicals are produced to create an escape route for the tumour and also reactive oxygen species are released by the inflammatory cells, causing further damage in their DNA.

In almost every cancer, inflammation can be observed [23] and the inflammatory environment of a tumour consequently leads to metastasis [24]. Several studies highlighted the anti-cancer activity of anti-inflammatory drugs which clearly shows the importance of inflammation in cancer [25].

Chronic inflammation is known to be one of the major indicators of cancer [23]. It induces neoplastic transformation of tissues and helps tumours develop further. Two pathways can be mentioned as underlying factors of inflammation in cancer: An intrinsic pathway which is related to genetic mutations that result in oncogene activation and tumor suppressor gene inactivation, an extrinsic pathway where inflammatory conditions are present, eventually causing cancer. Both of these pathways lead to the activation of various transcription factors such as NF-κB, STAT3, HIF1α in tumor cells which result in the expression of several chemokines, cytokines (such as IL-1β, IL-6, IL-23, and TNF-α), and prostaglandins. These factors are produced by immune system cells in the extrinsic pathway such as macrophages and by neoplastic cells in the intrinsic pathway which trigger inflammation further through the recruitment of leukocytes to the site of tumours. Following the activation of this inflammatory process, a vicious circle is created where reactive factors such as reactive oxygen species (ROS) cause tissue injury and persistent stimuli for regeneration [26].

Constant inflammatory signals trigger a developing tumour invasion with an alteration in tissue homeostasis. Additionally, cell stress molecules as well as apoptotic/necrotic compounds of both tumour and healthy cells -such as damage-associated

molecular patterns (DAMPS)- initiate the stimulation of macrophages and M2 polarization (alternatively activated macrophages) as well as fibroblast recruitment [27-29]. Other factors such as glucose concentrations, iNOS, hypoxia, TGF-β also cooperate in fibroblast recruitment and the activation of the fibrotic process which takes part in the progression of tumour microenvironment composition [30, 31].

Damage-associated molecular patterns (DAMPs) are endogenous molecules secreted by stressed cells undergoing necrosis and by extracellular matrix upon tissue damage. These molecules act as a danger signal that promotes an inflammatory response. Elevated levels of DAMPs are found to be linked with various inflammatory diseases such as arthritis and cancer [32].

In the tumour microenvironment, not only tumour cells but also infiltrated immune cells play a significant role in the progression of the disease. The interaction between DAMPs and Toll-like-receptors (TLRs) alters the regulation of cytokines [33]. And because the core of a tumour mass lacks oxygen and nutrition, cells undergo necrosis and constantly produce DAMPs. They are also produced upon immunogenic cell death and ECM degradation. These molecules interact with TLRs as well as macrophages and endothelial cells leading to the secretion of several cytokines that participate in tumour growth and metastasis [34]. Secretion of DAMPs activates TLRs further, causing more secretion of DAMPs and cytokines including several interleukins as well as TNF-α and TGF-β [35-37].

TLRs are membrane bound receptors and they recognise a wide range of DAMP molecules such as heat shock protein-60 (HSP60), MMP-2, and high mobility group box protein (HMGB1) which leads to the secretion of various pro-inflammatory mediators [33]. HMGB1 is the most abundantly produced DAMP molecule by dying tumour cells and it has a significant role in malignancies. It interacts with TLR4 in the oxidated state causing the secretion of cytokines. On the other hand, when it is in a reduced state, it binds to CXCL12 triggering chemotaxis *via* CXCR4 [38]. The significance of CXC receptors in cancer will be discussed in the next section.

It is well established that in a tumour microenvironment, many non-tumour cells are present along with cancer cells. Among these, macrophages are the major inflammatory components. When they are infiltrated into the tumour bed, they become tumour-associated macrophages or TAMs in short [29]. Researches have shown that TAMs are closely linked with tumour progression and angiogenesis. They express TLRs and are activated by DAMPs indicating their contribution to cancer cell invasion and metastasis [26, 39, 40]. It is thought that TAMs are derived from the circulating monocytes present in the blood. When a tumour develops, these monocytes relocate to its site first. Afterwards, they transform into TAMs and construct the largest immune population. In this process, T-cells with anti-tumour properties are also recalled which can destroy cancer cells. However, settled tumours manage to block their anti-tumour activities by enforcing a suppressive environment. On the other hand, macrophages encounter a similar fate. While they exhibit cytotoxic activities under normal circumstances, they become strongly possessed by cancerous cells in tumour bed leading to a complete differentiation in their functions. Consequently, they develop immuno-suppressive activity and participate in tumour progression [41]. Various studies reported a significant correlation between high levels of TAMs and aggressive tumours [39, 42, 43]. For instance, they produce growth factors like EGF, VGF, VEGF which help cancer cells proliferate directly and cytokines that activate certain pathways controlling cell apoptosis such as the STAT3 pathway by IL-6 [44, 45].

Under hypoxic conditions of cancerous tumours, macrophages produce various pro-angiogenic factors including CXCL8 (precursor of IL-8), PIGF (placental growth factor), Bv8 (prokineticin), and VEGF [46]. On the other hand, IL-10 and TGF-β are some of the other cytokines that show immunosuppressive activity inhibiting anti-tumour properties of T cells [47, 48] even though TGF-β can also display migration inhibiting activity in some cancers as will be discussed in the next section.

The chaotic circumstances that a tumour microenvironment generates influence even some of the healthy cells' functions including immune system cells, endothelial cells, and fibroblasts as well as

the compounds they express. Various studies confirmed that in tumour progression and metastasis, proteolytic enzymes and the extracellular matrix (ECM) components play a major role together with immune cells through building the inflammatory environment [49, 50].

The inflammation in the tumour bed also produces mutagenic factors that help develop tumour formation [24]. It is a major source for cell survival and growth along with pro-angiogenic factors and extracellular matrix remodeling enzymes that support invasion, metastasis, and angiogenesis [26].

Macrophages play a significant role in remodeling extracellular matrix through the production of certain enzymes such as MMPs and cathepsins. Remodeling of ECM along with ECM binding cytokines triggers inflammatory cell infiltration, angiogenesis, and tumour invasion. For instance, cathepsin B and S produced by TAMs can induce cancer spread and angiogenesis [51]. Furthermore, MMP-9 produced by TAMs plays an important role in skin cancer progression [52]. Experiments have shown that MMP-2 and -9 modulate the ECM *via* releasing VEGF that induces angiogenesis in pancreatic cancer [53, 54].

Immune cells have been a major focus of inflammation-related studies. It has been reported that mesenchymal stem cells (MSCs) and fibroblasts are crucial for the regulation of inflammatory response [55, 56]. MSCs exhibit strong suppressive activities through various mechanisms. One of these mechanisms involves ECM remodeling where MSCs trigger tumour progression through MMPs. One study reported that in ovarian cancer, MMP-2 and -9 produced by MSCs promote tumour invasion [57].

There are numerous other inflammatory factors and hundreds of articles published on their relations with different cancer types. In the next section, some of the major mediators and their activity on triggering MMP overexpression in cancer will be discussed.

1.2. Inflammation, MMPs, and Cancer

There is sufficient evidence indicating an important link between cancer and chronic inflammation. When exposed to infectious agents, tissues are infiltrated by immune cells, chemokines, cytokines, and growth factors that contribute to the metastasis of cancer cells [58, 59]. The participation of MMPs in inflammatory processes includes regulation of physical barriers, modulation of inflammatory mediators such as chemokines and cytokines, helping chemokines form a gradient in damaged tissues that recall leukocytes to the infectious or injured area [60, 61].

Chemokine receptors belong to the G protein-coupled receptor superfamily and display several functions in cancer progression [62]. One of these receptors known as C-C motif chemokine receptor-10 (CCR10) is produced by plasma cells, melanocytes, and skin-resident T cells [63]. It can be stimulated by CCL27 and CCL28 chemokines [64]. The interaction between CCR10 and CCL27 is involved in T-cell mediated skin inflammation [65]. Several studies highlighted the contribution of CCR10 to cell growth and migration in many tumours such as melanoma [66], glioblastoma [67], and squamous cell carcinoma [68]. One recent study performed on multiple breast cancer cell lines (MCF-7, BT-474, and MDA-MB-231) investigated the influence of CCR10-CCL27 interaction on cell migration and its mechanism. Results indicated that CCR10 is highly expressed in all these cell lines and it is associated with capsular invasion as well as lymph node metastasis. Additionally, stimulation of CCL27 dose-dependently led to the activation of the ERK1/2 pathway and therefore overexpression of MMP-7 resulting in cell invasion and migration [69].

CXC chemokine receptors belong to a G-protein superfamily known as chemokine receptors. They can induce chemotaxis which contributes to the progression of various diseases. Among these receptors, CXCR3 has been found in many tumours. It can be activated by several chemokines such as CXCL9, 10, 11, and 14 [70]. Studies reported the involvement of CXCR3 in colorectal cancer [71], basal cell carcinoma [72], and breast cancer [73, 74]. Additionally, its overexpression has been found closely related to renal cell carcinoma metastasis [75] as well as lymph node metastasis of lung adenocarcinoma [76]. Furthermore, a recent study demonstrated that in gastric cancer, CXCR3 activated by CXCL10 triggers cell inva-

sion and migration *via* PI3K/Akt pathway activation and upregulation of MMP-2 and MMP-9 [77].

Supporting evidence revealed that immune responses can be modulated by neutrophils in the tumour microenvironment which can lead to tumour development [78]. Neutrophils can interact with cells, cytotoxic mediators, ECM as well as the release of MMPs. Among these, MMP-9 significantly contributes to tissue damage and inflammation through proteolytic cleavages leading to ECM degradation and cytokines/chemokines activation. Previous studies demonstrated that collagen breakdown by MMP-8 and 9 and the cleavage of a prolyl endopeptidase afterwards, generate a tripeptide known as N-acetyl-proline-glycine-prolyine (ac-PGP) [79, 80]. This tripeptide has been shown to bind CXCR2, a receptor of IL-8 and a powerful neutrophil chemotactic factor. This process triggers the chemotaxis of inflammatory cells to the site of tumour [81, 82]. One study conducted on non-small cell lung cancer tissues revealed a correlation between CXCR2 expression and tumour inflammation as well as angiogenesis [83]. Additionally, it has been reported that in breast cancer cells, CXCR2 plays a significant role in tumour invasion and metastasis to lung tissues [84]. However, CXCR2 is not only expressed by neutrophils. It is also produced by a wide range of tumours including ovarian, pancreatic, lung, melanoma tissues which indicates a potential role of ac-PGP tripeptide in tumour cell chemoattraction [83, 85].

In a recent study, the role of inflammation-generated extracellular matrix fragments (ac-PGP) on tumor cells disseminating to lung parenchyma was investigated in mice with mammary and melanoma tumours. Exposure to cigarette smoke and lipopolysaccharide led to neutrophil accumulation in the lungs causing a high level of MMP-9 expression and therefore allowing the release of ac-PGP tripeptides which attracted tumour cells to the lung parenchyma. On the other hand, MMP-9 negative mice exhibited a decreased level of ac-PGP. Additionally, silencing CXCR2 on tumour cells indicated that the chemoattractant effect of ac-PGP is dependent on the presence of CXCR2 as well. These results show a significant role of MMP-9 in cancer metastasis with the contribution of inflammatory mediators [86].

Experimental evidence revealed that CXCL12–CXCR4 interaction elevated active MMP-9 expression in several human cancer cell lines including colorectal cancer cells, head and neck squamous cell carcinoma cells as well as nasopharyngeal carcinoma cells [87-89]. Researchers also investigated the correlation between tumour progression in breast cancer and the expression of CXCR4, VEGF, and MMP-9. They discovered that the expression of CXCR4 was 61% higher than in normal tissues while VEGF expression was higher by 68% and MMP-9 by 63% and each of these markers correlates with tumour progression. Moreover, combined elevated expression of any two of these markers was observed to be highly associated with lymph node metastasis in breast cancer [90].

IL-17 is a cytokine family produced by a subgroup of T helper cells (Th17). They play significant roles in inflammatory diseases and cancers [91, 92]. There are six members in this family named IL-17A, -B, -C, -D, -E, and -F. The way in which IL-17 members exhibit their activity is through binding to their receptor family known as IL-17R [93]. Studies revealed that in various tumours, these receptors are overexpressed [94, 95]. One of these receptors, IL-17RB has been observed in several tumours. According to a study conducted on gastric cancer tissues, the expression of IL-17RB increases significantly and it is closely associated with poor prognosis in patients [96]. Additionally, it has been reported that overexpression of IL-17RB plays an important role in the metastasis of pancreatic and prostate cancers [97, 98].

Recent experiments demonstrated that IL-17B can directly stimulate the invasion, growth, and migration of thyroid cancer cells. It can also contribute to tumour invasion and metastasis of thyroid cancer by stimulating the ERK1/2 pathway time- and dose-dependently. Activation of the ERK1/2 pathway promotes the expression of MMP-9 suggesting IL-17B upregulates MMP-9 expression *via* IL-17RB/ERK1/2 pathway [99].

Similarly, IL-17A has been reported to induce overexpression of MMP-9 and therefore cell invasiveness in esophageal adenocarcinoma [100].

Interleukin-1α (IL-1α) is a member of the IL-1 cytokine family that participates in the regulation

of immune and inflammatory responses. It is widely found in the tumour microenvironment with tumour-promoting effects [101, 102]. According to a recent study on pancreatic ductal adenocarcinoma (PDAC), IL-1α is highly expressed and it plays an important role in cell invasion and migration [103]. Furthermore, MMPs are significantly upregulated in PDAC by pancreatic stellate cells, a major producer and regulator of the ECM, while their inhibitor TIMP3 is downregulated [104]. As mentioned in the previous part, TGF-β is a growth factor with both pro-tumour activity (in the early stages of some cancers) and anti-tumour functions (usually in the late stages). Results obtained revealed that in PDAC, IL-1α induces a specific MMP/TIMP profile leading to overexpression of MMP-1 and MMP-3 whereas TGF-β acts as a migration suppressor through inhibiting MMP overexpression [103].

IL-5 is a T-cell derived cytokine essential for eosinophil activation, differentiation as well as B-cell differentiation [105, 106]. It can induce B-cell proliferation through activating PI3K, Jak2, Btk tyrosine kinases, and HS1 [107]. In a recent study, the roles of IL-5 and its receptor IL-5Rα on cell migration in muscle-invasive bladder carcinoma (MIBC) cell lines have been investigated. Results have shown that the expression levels of both IL-5 and IL-5Rα are increased compared to healthy cells. Additionally, IL-5 has been observed to induce the expression of MMP-9 *via* activating transcription factors NF-κB and AP-1 causing cell motility and migration of bladder cancer cells. Experiments also revealed that IL-5 induces ERK1/2 signaling which mediates MMP-9 expression [108]. A similar study was conducted on 5637 bladder cancer cells investigating the role of IL-15 which is a key regulator of lymphocyte activation and differentiation. Results revealed that IL-15 promotes the expression of MMP-9 and activates NF-κB through ERK1/2 signaling leading to cell migration and invasion [109].

Arachidonic acid derivatives are known to participate in inflammation, pain, and fever and they are found to be closely linked with tumour development as well. Among those, COX-1 is present on a stable level in nearly all tissues whereas COX-2 is observed highly expressed in hyperplastic tissues such as breast cancer, lung cancer, and gastric cancer [110-112]. In a study conducted on oral squamous cell carcinoma (OSCC), the expression level of COX-2 and MMP-7 were investigated. Experiments revealed that mRNA expressions of both COX-2 and MMP-7 were positively correlated in OSCC indicating a close relationship between these two genes [113].

As mentioned in the previous section, TAMs are transformed monocytes with significant roles in tumour progression. It was reported that TAMs infiltrate into tumour area abundantly which is then associated with metastasis and angiogenesis [114-116]. On the other hand, MMPs are well known to be significant in chronic inflammation, tissue remodeling, and cancer progression. In a study conducted on ovarian cancer cells, the function of TAMs on the expression of MMP-2, MMP-9, and MMP-10 was investigated. Results have shown that TAMs upregulate the production of these three MMPs through activating NF-κB, MAPK signaling, and TLR signaling pathways which indicates the significance of the TAM-MMP relationship in ovarian cancer progression and invasion [117].

Nuclear factor of activated T cell (NFAT) proteins is a family of transcription factors expressed in most immune system cells. They play a crucial role in the transcription of cytokine genes as well as other genes necessary for immune response. They also regulate T cell development and differentiation and bind interleukin-2 (IL-2) promoter in activated T cells [118-121]. However, NFAT genes participate in many other physiological processes as well. Various studies have shown that NFAT genes take part in cancer development and progression *via* regulating cell proliferation, migration, invasion, and angiogenesis [122-125]. The first identified member of this family, NFAT1, has been found highly expressed in several cancers such as breast cancer [126], melanoma [127, 128] and lung cancer [129]. The mechanism through which NFAT1 contributes to tumour growth and metastasis has been reported to be associated with the expression of its target genes including COX-2, MDM-2, IL-8, and MMP-3 [126, 128, 130]. A recent study performed on esophageal squamous cell carcinoma (ESCC) demonstrated that NFAT1

supports metastasis of ESCC cells through regulation of MMP-3 and silencing this gene could prevent cells from migrating [131].

Tumour necrosis factor-alfa (TNF-α) is an important pro-inflammatory cytokine. Elevated expression of TNF-α is observed in several autoimmune diseases such as rheumatoid arthritis and multiple sclerosis [132]. It is produced by T-cells and macrophages as a membrane bound protein and is activated by TNF-converting enzymes [133, 134]. Several studies mentioned the significance of TNF-α induced MMPs and their expression in cancer [135, 136]. Multiple pathways can be involved in this process. For instance, in 5637 bladder cancer tissues, experiments showed that TNF-α induces MMP-9 expression through the p38 MAPK pathway [137].

The double-stranded RNA-dependent protein kinase (PKR) is a serine/threonine kinase. It is activated by homodimerization and autophosphorylation and participates in inflammatory responses against infectious factors through inducing NF-κB activation [138]. Furthermore, it has been revealed that PKR mediates the activation of MMP-2 and MMP-9 induced by TNF-α [139] as well as MMP-13 [140]. On the other hand, MMP-13 has been found overly expressed in gastric cancer [141], giant cell tumor (GCT) [142], osteosarcoma [143], and head and neck squamous cell carcinoma [144]. Available data indicate that elevated expression of MMPs mediated by PKR contributes to cancer progression suggesting that PKR could be considered a target in cancer studies.

Even though most MMPs are found overexpressed where inflammation is present, some of them can display anti-inflammatory effects as well. In a study conducted on irreversible pulpitis of mature erupted teeth, treatment with MMP-3 resulted in a decrease in the number of inflammatory cells such as macrophages while it also inhibited IL-6 expression significantly. On the other hand, the inhibition of MMP-3 activity terminated these effects [145]. Furthermore, McMillan *et al*. investigated the role of MMP-9 in allergen-induced airway inflammation *in vivo*. They observed that in the absence of MMP-9, inflammatory cell recruitment significantly increases as well as the levels of cytokines such as IL-4, IL-13, and macrophage-derived chemokine CCL-22, leading to enhanced pulmonary inflammation [146]. Additionally, MMP-19 deficiency in inflammatory bowel disease caused persistent inflammation and poor recovery in a study conducted by Brauer *et al*. [147]. Similarly, MMP-10 has been observed to restrict the pro-inflammatory activity of macrophages in mice with lung infection [148]. However, there is not enough literature on the anti-inflammatory roles of MMPs in cancer.

CONCLUSION

Understanding the mechanism of cancer formation and how it develops is the key to finding revolutionary approaches in therapy. The purpose of this review is to enlighten some aspects of the ways through which cancer cells find an escape route using their inflammatory microenvironment with the contribution of MMPs. Overall data have shown a strong relationship between MMP overexpression by inflammatory mediators and cancer progression. Hence, targetting specific molecules involved in this process could be considered as a potential treatment strategy.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Bakar-Ates F contributed to design, literature search, and review of the collected data. Ozkan E contributed to literature search and reporting data.

REFERENCES

[1] Visse, R.; Nagase, H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ. Res.,* **2003**, *92*(8), 827-839. http://dx.doi.org/10.1161/01.RES.0000070112.80711.3D PMID: 12730128

[2] Nagase, H.; Woessner, J.F., Jr Matrix metalloproteinases. *J. Biol. Chem.,* **1999**, *274*(31), 21491-21494. http://dx.doi.org/10.1074/jbc.274.31.21491 PMID: 10419448

[3] Sbardella, D.; Fasciglione, G.F.; Gioia, M.; Ciaccio, C.; Tundo, G.R.; Marini, S.; Coletta, M. Human matrix metalloproteinases: an ubiquitarian class of enzymes involved in several pathological processes. *Mol. Aspects Med.,* **2012**, *33*(2), 119-208. http://dx.doi.org/10.1016/j.mam.2011.10.015 PMID: 22100792

[4] Gordon, J.L.; Drummond, A.H.; Galloway, W.A. Metalloproteinase inhibitors as therapeutics. *Clin. Exp. Rheumatol.,* **1993**, *11*(Suppl. 8), S91-S94. PMID: 8391953

[5] Ennis, B.W.; Matrisian, L.M. Matrix degrading metalloproteinases. *J. Neurooncol.,* **1994**, *18*(2), 105-109. http://dx.doi.org/10.1007/BF01050416 PMID: 7964973

[6] Galis, Z.S.; Sukhova, G.K.; Lark, M.W.; Libby, P. Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. *J. Clin. Invest.,* **1994**, *94*(6), 2493-2503. http://dx.doi.org/10.1172/JCI117619 PMID: 7989608

[7] McDonnell, S.; Morgan, M.; Lynch, C. Role of matrix metalloproteinases in normal and disease processes. *Biochem. Soc. Trans.,* **1999**, *27*(4), 734-740. http://dx.doi.org/10.1042/bst0270734 PMID: 10917674

[8] Gialeli, C.; Theocharis, A.D.; Karamanos, N.K. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. *FEBS J.,* **2011**, *278*(1), 16-27. http://dx.doi.org/10.1111/j.1742-4658.2010.07919.x PMID: 21087457

[9] Abdelazim, I.A.; Abufaza, M.L.; Al-Kadi, M. Immunoexpression of matrix metalloproteinase-2 in epithelial ovarian cancers. *Asian Pac. J. Reprod.,* **2013**, *2*(2), 136-141. http://dx.doi.org/10.1016/S2305-0500(13)60134-7

[10] Adley, B.P.; Gleason, K.J.; Yang, X.J.; Stack, M.S. Expression of membrane type 1 matrix metalloproteinase (MMP-14) in epithelial ovarian cancer: high level expression in clear cell carcinoma. *Gynecol. Oncol.,* **2009**, *112*(2), 319-324. http://dx.doi.org/10.1016/j.ygyno.2008.09.025 PMID: 18976802

[11] Brinckerhoff, C.E.; Rutter, J.L.; Benbow, U. Interstitial collagenases as markers of tumor progression. *Clin. Cancer Res.,* **2000**, *6*(12), 4823-4830. PMID: 11156241

[12] Hofmann, H.S.; Hansen, G.; Richter, G.; Taege, C.; Simm, A.; Silber, R.E.; Burdach, S. Matrix metalloproteinase-12 expression correlates with local recurrence and metastatic disease in non-small cell lung cancer patients. *Clin. Cancer Res.,* **2005**, *11*(3), 1086-1092. PMID: 15709175

[13] Ding, Y.; Shimada, Y.; Gorrin-Rivas, M.J.; Itami, A.; Li, Z.; Hong, T.; Maeda, M.; Komoto, I.; Kawabe, A.; Kaganoi, J.; Imamura, M. Clinicopathological significance of human macrophage metalloelastase expression in esophageal squamous cell carcinoma. *Oncology,* **2002**, *63*(4), 378-384. http://dx.doi.org/10.1159/000066231 PMID: 12417793

[14] Schveigert, D.; Cicenas, S.; Bruzas, S.; Samalavicius, N.E.; Gudleviciene, Z.; Didziapetriene, J. The value of MMP-9 for breast and non-small cell lung cancer patients' survival. *Adv. Med. Sci.,* **2013**, *58*(1), 73-82. http://dx.doi.org/10.2478/v10039-012-0066-y PMID: 23640949

[15] Wang, J.; Shi, Q.; Yuan, T.X.; Song, Q.L.; Zhang, Y.; Wei, Q.; Zhou, L.; Luo, J.; Zuo, G.; Tang, M.; He, T.C.; Weng, Y. Matrix metalloproteinase 9 (MMP-9) in osteosarcoma: review and meta-analysis. *Clin. Chim. Acta,* **2014**, *433*, 225-231. http://dx.doi.org/10.1016/j.cca.2014.03.023 PMID: 24704305

[16] Araújo, R.F., Jr; Lira, G.A.; Vilaça, J.A.; Guedes, H.G.; Leitão, M.C.A.; Lucena, H.F.; Ramos, C.C.O. Prognostic and diagnostic implications of MMP-2, MMP-9, and VEGF-α expressions in colorectal cancer. *Pathol. Res. Pract.,* **2015**, *211*(1), 71-77. http://dx.doi.org/10.1016/j.prp.2014.09.007 PMID: 25446246

[17] Fan, D.; Wang, Y.; Qi, P.; Chen, Y.; Xu, P.; Yang, X.; Jin, X.; Tian, X. MicroRNA-183 functions as the tumor suppressor *via* inhibiting cellular invasion and metastasis by targeting MMP-9 in cervical cancer. *Gynecol. Oncol.,* **2016**, *141*(1), 166-174. http://dx.doi.org/10.1016/j.ygyno.2016.02.006 PMID: 26873866

[18] Ahmed Haji Omar, A.; Haglund, C.; Virolainen, S.; Häyry, V.; Atula, T.; Kontio, R.; Salo, T.; Sorsa, T.; Hagström, J. MMP-7, MMP-8, and MMP-9 in oral and cutaneous squamous cell carcinomas. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol.,* **2015**, *119*(4), 459-467. http://dx.doi.org/10.1016/j.oooo.2014.12.019 PMID: 25697929

[19] Rodriguez-Manzaneque, J.C.; Lane, T.F.; Ortega, M.A.; Hynes, R.O.; Lawler, J.; Iruela-Arispe, M.L. Thrombospondin-1 suppresses spontaneous tumor growth and inhibits activation of matrix metalloproteinase-9 and mobilization of vascular endothelial growth factor. *Proc. Natl. Acad. Sci. USA,* **2001**, *98*(22), 12485-12490. http://dx.doi.org/10.1073/pnas.171460498 PMID: 11606713

[20] Colotta, F.; Allavena, P.; Sica, A.; Garlanda, C.; Mantovani, A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis,* **2009**, *30*(7), 1073-1081. http://dx.doi.org/10.1093/carcin/bgp127 PMID: 19468060

[21] Medzhitov, R. Origin and physiological roles of inflammation. *Nature,* **2008**, *454*(7203), 428-435. http://dx.doi.org/10.1038/nature07201 PMID: 18650913

[22] Schäfer, M.; Werner, S. Cancer as an overhealing wound: an old hypothesis revisited. *Nat. Rev. Mol. Cell Biol.,* **2008**, *9*(8), 628-638. http://dx.doi.org/10.1038/nrm2455 PMID: 18628784

[23] Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: the next generation. *Cell,* **2011**, *144*(5), 646-674. http://dx.doi.org/10.1016/j.cell.2011.02.013 PMID: 21376230

[24] Grivennikov, S.I.; Greten, F.R.; Karin, M. Immunity, inflammation, and cancer. *Cell,* **2010**, *140*(6), 883-899. http://dx.doi.org/10.1016/j.cell.2010.01.025 PMID: 20303878

[25] Pribluda, A.; Elyada, E.; Wiener, Z.; Hamza, H.; Goldstein, R.E.; Biton, M.; Burstain, I.; Morgenstern, Y.; Brachya, G.; Billauer, H.; Biton, S.; Snir-Alkalay, I.; Vucic, D.; Schlereth, K.; Mernberger, M.; Stiewe, T.; Oren, M.; Alitalo, K.; Pikarsky, E.; Ben-Neriah, Y. A senescence-inflammatory switch from cancer-inhibitory to cancer-promoting mechanism. *Cancer Cell,* **2013**, *24*(2), 242-256. http://dx.doi.org/10.1016/j.ccr.2013.06.005 PMID: 23890787

[26] Mantovani, A.; Allavena, P.; Sica, A.; Balkwill, F. Cancer-related inflammation. *Nature,* **2008**, *454*(7203), 436-444. http://dx.doi.org/10.1038/nature07205 PMID: 18650914

[27] Brenner, C.; Galluzzi, L.; Kepp, O.; Kroemer, G. Decoding cell death signals in liver inflammation. *J. Hepatol.,* **2013**, *59*(3), 583-594. http://dx.doi.org/10.1016/j.jhep.2013.03.033 PMID: 23567086

[28] Weisser, S.B.; McLarren, K.W.; Kuroda, E.; Sly, L.M. Generation and characterization of murine alternatively activated macrophages. *Methods Mol. Biol.,* **2013**, *946*, 225-239. http://dx.doi.org/10.1007/978-1-62703-128-8_14 PMID: 23179835

[29] Komohara, Y.; Takeya, M. CAFs and TAMs: maestros of the tumour microenvironment. *J. Pathol.,* **2017**, *241*(3), 313-315. http://dx.doi.org/10.1002/path.4824 PMID: 27753093

[30] Hu, W.; Jiang, Z.; Zhang, Y.; Liu, Q.; Fan, J.; Luo, N.; Dong, X.; Yu, X. Characterization of infiltrating macrophages in high glucose-induced peritoneal fibrosis in rats. *Mol. Med. Rep.,* **2012**, *6*(1), 93-99. PMID: 22552745

[31] Cieslik, K.A.; Trial, J.; Entman, M.L. Mesenchymal stem cell-derived inflammatory fibroblasts promote monocyte transition into myeloid fibroblasts *via* an IL-6-dependent mechanism in the aging mouse heart. *FASEB J.,* **2015**, *29*(8), 3160-3170. http://dx.doi.org/10.1096/fj.14-268136 PMID: 25888601

[32] Pisetsky, D.S.; Erlandsson-Harris, H.; Andersson, U. High-mobility group box protein 1 (HMGB1): an alarmin mediating the pathogenesis of rheumatic disease. *Arthritis Res. Ther.,* **2008**, *10*(3), 209. http://dx.doi.org/10.1186/ar2440 PMID: 18598385

[33] Patidar, A.; Selvaraj, S.; Sarode, A.; Chauhan, P.; Chattopadhyay, D.; Saha, B. DAMP-TLR-cytokine axis dictates the fate of tumor. *Cytokine,* **2018**, *104*, 114-123. http://dx.doi.org/10.1016/j.cyto.2017.10.004 PMID: 29032985

[34] Hernandez, C.; Huebener, P.; Schwabe, R.F. Damage-associated molecular patterns in cancer: a double-edged sword. *Oncogene,* **2016**, *35*(46), 5931-5941. http://dx.doi.org/10.1038/onc.2016.104 PMID: 27086930

[35] Oshima, H.; Oshima, M. The inflammatory network in the gastrointestinal tumor microenvironment: lessons from mouse models. *J. Gastroenterol.,* **2012**, *47*(2), 97-106. http://dx.doi.org/10.1007/s00535-011-0523-6 PMID: 22218775

[36] Yan, J.; Hua, F.; Liu, H.Z.; Yang, H.Z.; Hu, Z.W. Simultaneous TLR2 inhibition and TLR9 activation synergistically suppress tumor metastasis in mice. *Acta Pharmacol. Sin.,* **2012**, *33*(4), 503-512. http://dx.doi.org/10.1038/aps.2011.193 PMID: 22426694

[37] Huang, Z.; Yang, Y.; Jiang, Y.; Shao, J.; Sun, X.; Chen, J.; Dong, L.; Zhang, J. Anti-tumor immune responses of tumor-associated macrophages *via* toll-like receptor 4 triggered by cationic polymers. *Biomaterials,* **2013**, *34*(3), 746-755. http://dx.doi.org/10.1016/j.biomaterials.2012.09.062 PMID: 23107297

[38] Magna, M.; Pisetsky, D.S. The role of HMGB1 in the pathogenesis of inflammatory and autoimmune diseases. *Mol. Med.,* **2014**, *20*, 138-146. http://dx.doi.org/10.2119/molmed.2013.00164 PMID: 24531836

[39] Bingle, L.; Brown, N.J.; Lewis, C.E. The role of tumour-associated macrophages in tumour progression: implications for new anticancer therapies. *J. Pathol.,* **2002**, *196*(3), 254-265. http://dx.doi.org/10.1002/path.1027 PMID: 11857487

[40] Kitamura, T.; Qian, B.Z.; Pollard, J.W. Immune cell promotion of metastasis. *Nat. Rev. Immunol.,* **2015**, *15*(2), 73-86. http://dx.doi.org/10.1038/nri3789 PMID: 25614318

[41] Allavena, P.; Mantovani, A. Immunology in the clinic review series; focus on cancer: tumour-associated macrophages: undisputed stars of the inflammatory tumour microenvironment. *Clin. Exp. Immunol.,* **2012**, *167*(2), 195-205. http://dx.doi.org/10.1111/j.1365-2249.2011.04515.x PMID: 22235995

[42] Finak, G.; Bertos, N.; Pepin, F.; Sadekova, S.; Souleimanova, M.; Zhao, H.; Chen, H.; Omeroglu, G.; Meterissian, S.; Omeroglu, A.; Hallett, M.; Park, M.

Stromal gene expression predicts clinical outcome in breast cancer. *Nat. Med.,* **2008**, *14*(5), 518-527. http://dx.doi.org/10.1038/nm1764 PMID: 18438415

[43] Sawa-Wejksza, K.; Kandefer-Szerszeń, M. Tumor-associated macrophages as target for antitumor therapy. *Arch. Immunol. Ther. Exp. (Warsz.),* **2018**, *66*(2), 97-111. http://dx.doi.org/10.1007/s00005-017-0480-8 PMID: 28660349

[44] Condeelis, J.; Pollard, J.W. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. *Cell,* **2006**, *124*(2), 263-266. http://dx.doi.org/10.1016/j.cell.2006.01.007 PMID: 16439202

[45] Hadjidaniel, M.D.; Muthugounder, S.; Hung, L.T.; Sheard, M.A.; Shirinbak, S.; Chan, R.Y.; Nakata, R.; Borriello, L.; Malvar, J.; Kennedy, R.J.; Iwakura, H.; Akamizu, T.; Sposto, R.; Shimada, H.; DeClerck, Y.A.; Asgharzadeh, S. Tumor-associated macrophages promote neuroblastoma *via* STAT3 phosphorylation and up-regulation of c-MYC. *Oncotarget,* **2017**, *8*(53), 91516-91529. http://dx.doi.org/10.18632/oncotarget.21066 PMID: 29207662

[46] Rolny, C.; Mazzone, M.; Tugues, S.; Laoui, D.; Johansson, I.; Coulon, C.; Squadrito, M.L.; Segura, I.; Li, X.; Knevels, E.; Costa, S.; Vinckier, S.; Dresselaer, T.; Åkerud, P.; De Mol, M.; Salomäki, H.; Phillipson, M.; Wyns, S.; Larsson, E.; Buysschaert, I.; Botling, J.; Himmelreich, U.; Van Ginderachter, J.A.; De Palma, M.; Dewerchin, M.; Claesson-Welsh, L.; Carmeliet, P. HRG inhibits tumor growth and metastasis by inducing macrophage polarization and vessel normalization through downregulation of PlGF. *Cancer Cell,* **2011**, *19*(1), 31-44. http://dx.doi.org/10.1016/j.ccr.2010.11.009 PMID: 21215706

[47] Coussens, L.M.; Zitvogel, L.; Palucka, A.K. Neutralizing tumor-promoting chronic inflammation: a magic bullet? *Science,* **2013**, *339*(6117), 286-291. http://dx.doi.org/10.1126/science.1232227 PMID: 23329041

[48] Mantovani, A.; Vecchi, A.; Allavena, P. Pharmacological modulation of monocytes and macrophages. *Curr. Opin. Pharmacol.,* **2014**, *17*, 38-44. http://dx.doi.org/10.1016/j.coph.2014.07.004 PMID: 25062123

[49] Caja, F.; Vannucci, L. TGFβ: A player on multiple fronts in the tumor microenvironment. *J. Immunotoxicol.,* **2015**, *12*(3), 300-307. http://dx.doi.org/10.3109/1547691X.2014.945667 PMID: 25140864

[50] Vannucci, L. Stroma as an active player in the development of the tumor microenvironment. *Cancer Microenviron.,* **2015**, *8*(3), 159-166. http://dx.doi.org/10.1007/s12307-014-0150-x PMID: 25106539

[51] Gocheva, V.; Wang, H.W.; Gadea, B.B.; Shree, T.; Hunter, K.E.; Garfall, A.L.; Berman, T.; Joyce, J.A. IL-4 induces cathepsin protease activity in tumor-associated macrophages to promote cancer growth and invasion. *Genes Dev.,* **2010**, *24*(3), 241-255. http://dx.doi.org/10.1101/gad.1874010 PMID: 20080943

[52] Coussens, L.M.; Tinkle, C.L.; Hanahan, D.; Werb, Z. MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. *Cell,* **2000**, *103*(3), 481-490. http://dx.doi.org/10.1016/S0092-8674(00)00139-2 PMID: 11081634

[53] Bergers, G.; Brekken, R.; McMahon, G.; Vu, T.H.; Itoh, T.; Tamaki, K.; Tanzawa, K.; Thorpe, P.; Itohara, S.; Werb, Z.; Hanahan, D. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. *Nat. Cell Biol.,* **2000**, *2*(10), 737-744. http://dx.doi.org/10.1038/35036374 PMID: 11025665

[54] Wang, F.; Jin, R.; Zou, B.B.; Li, L.; Cheng, F.W.; Luo, X.; Geng, X.; Zhang, S.Q. Activation of Toll-like receptor 7 regulates the expression of IFN-λ1, p53, PTEN, VEGF, TIMP-1 and MMP-9 in pancreatic cancer cells. *Mol. Med. Rep.,* **2016**, *13*(2), 1807-1812. http://dx.doi.org/10.3892/mmr.2015.4730 PMID: 26718740

[55] Brennen, W.N.; Denmeade, S.R.; Isaacs, J.T. Mesenchymal stem cells as a vector for the inflammatory prostate microenvironment. *Endocr. Relat. Cancer,* **2013**, *20*(5), R269-R290. http://dx.doi.org/10.1530/ERC-13-0151 PMID: 23975882

[56] Ma, S.; Xie, N.; Li, W.; Yuan, B.; Shi, Y.; Wang, Y. Immunobiology of mesenchymal stem cells. *Cell Death Differ.,* **2014**, *21*(2), 216-225. http://dx.doi.org/10.1038/cdd.2013.158 PMID: 24185619

[57] Chu, Y.; Tang, H.; Guo, Y.; Guo, J.; Huang, B.; Fang, F.; Cai, J.; Wang, Z. Adipose-derived mesenchymal stem cells promote cell proliferation and invasion of epithelial ovarian cancer. *Exp. Cell Res.,* **2015**, *337*(1), 16-27. http://dx.doi.org/10.1016/j.yexcr.2015.07.020 PMID: 26209607

[58] Fridlender, Z.G.; Sun, J.; Kim, S.; Kapoor, V.; Cheng, G.; Ling, L.; Worthen, G.S.; Albelda, S.M. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" *versus* "N2" TAN. *Cancer Cell,* **2009**, *16*(3), 183-194. http://dx.doi.org/10.1016/j.ccr.2009.06.017 PMID: 19732719

[59] Sica, A.; Mantovani, A. Macrophage plasticity and polarization: *in vivo* veritas. *J. Clin. Invest.,* **2012**, *122*(3), 787-795. http://dx.doi.org/10.1172/JCI59643 PMID: 22378047

[60] McQuibban, G.A.; Butler, G.S.; Gong, J.H.; Bendall, L.; Power, C.; Clark-Lewis, I.; Overall, C.M. Matrix metalloproteinase activity inactivates the CXC chemokine stromal cell-derived factor-1. *J. Biol. Chem.,* **2001**, *276*(47), 43503-43508.

http://dx.doi.org/10.1074/jbc.M107736200
PMID: 11571304

[61] Li, Q.; Park, P.W.; Wilson, C.L.; Parks, W.C. Matrilysin shedding of syndecan-1 regulates chemokine mobilization and transepithelial efflux of neutrophils in acute lung injury. *Cell,* **2002**, *111*(5), 635-646.
http://dx.doi.org/10.1016/S0092-8674(02)01079-6
PMID: 12464176

[62] Mantovani, A.; Savino, B.; Locati, M.; Zammataro, L.; Allavena, P.; Bonecchi, R. The chemokine system in cancer biology and therapy. *Cytokine Growth Factor Rev.,* **2010**, *21*(1), 27-39.
http://dx.doi.org/10.1016/j.cytogfr.2009.11.007
PMID: 20004131

[63] Moed, H.; Boorsma, D.M.; Tensen, C.P.; Flier, J.; Jonker, M.J.; Stoof, T.J.; von Blomberg, B.M.; Bruynzeel, D.P.; Scheper, R.J.; Rustemeyer, T.; Gibbs, S. Increased CCL27-CCR10 expression in allergic contact dermatitis: implications for local skin memory. *J. Pathol.,* **2004**, *204*(1), 39-46.
http://dx.doi.org/10.1002/path.1619 PMID: 15307136

[64] Xiong, N.; Fu, Y.; Hu, S.; Xia, M.; Yang, J. CCR10 and its ligands in regulation of epithelial immunity and diseases. *Protein Cell,* **2012**, *3*(8), 571-580.
http://dx.doi.org/10.1007/s13238-012-2927-3 PMID: 22684736

[65] Homey, B.; Alenius, H.; Müller, A.; Soto, H.; Bowman, E.P.; Yuan, W.; McEvoy, L.; Lauerma, A.I.; Assmann, T.; Bünemann, E.; Lehto, M.; Wolff, H.; Yen, D.; Marxhausen, H.; To, W.; Sedgwick, J.; Ruzicka, T.; Lehmann, P.; Zlotnik, A. CCL27-CCR10 interactions regulate T cell-mediated skin inflammation. *Nat. Med.,* **2002**, *8*(2), 157-165.
http://dx.doi.org/10.1038/nm0202-157
PMID: 11821900

[66] Kühnelt-Leddihn, L.; Müller, H.; Eisendle, K.; Zelger, B.; Weinlich, G. Overexpression of the chemokine receptors CXCR4, CCR7, CCR9, and CCR10 in human primary cutaneous melanoma: a potential prognostic value for CCR7 and CCR10? *Arch. Dermatol. Res.,* **2012**, *304*(3), 185-193.
http://dx.doi.org/10.1007/s00403-012-1222-8 PMID: 22350183

[67] Chen, L.; Liu, X.; Zhang, H.Y.; Du, W.; Qin, Z.; Yao, Y.; Mao, Y.; Zhou, L. Upregulation of chemokine receptor CCR10 is essential for glioma proliferation, invasion and patient survival. *Oncotarget,* **2014**, *5*(16), 6576-6583.
http://dx.doi.org/10.18632/oncotarget.2134
PMID: 25149529

[68] Kai, H.; Kadono, T.; Kakinuma, T.; Tomita, M.; Ohmatsu, H.; Asano, Y.; Tada, Y.; Sugaya, M.; Sato, S. CCR10 and CCL27 are overexpressed in cutaneous squamous cell carcinoma. *Pathol. Res. Pract.,* **2011**, *207*(1), 43-48.
http://dx.doi.org/10.1016/j.prp.2010.10.007
PMID: 21144674

[69] Lin, H.Y.; Sun, S.M.; Lu, X.F.; Chen, P.Y.; Chen, C.F.; Liang, W.Q.; Peng, C.Y. CCR10 activation stimulates the invasion and migration of breast cancer cells through the ERK1/2/MMP-7 signaling pathway. *Int. Immunopharmacol.,* **2017**, *51*, 124-130.
http://dx.doi.org/10.1016/j.intimp.2017.07.018 PMID: 28830025

[70] Fulton, A.M. The chemokine receptors CXCR4 and CXCR3 in cancer. *Curr. Oncol. Rep.,* **2009**, *11*(2), 125-131.
http://dx.doi.org/10.1007/s11912-009-0019-1 PMID: 19216844

[71] Wu, Z.; Han, X.; Yan, J.; Pan, Y.; Gong, J.; Di, J.; Cheng, Z.; Jin, Z.; Wang, Z.; Zheng, Q.; Wang, Y. The prognostic significance of chemokine receptor CXCR3 expression in colorectal carcinoma. *Biomed. Pharmacother.,* **2012**, *66*(5), 373-377.
http://dx.doi.org/10.1016/j.biopha.2011.12.003
PMID: 22401929

[72] Lo, B.K.; Yu, M.; Zloty, D.; Cowan, B.; Shapiro, J.; McElwee, K.J. CXCR3/ligands are significantly involved in the tumorigenesis of basal cell carcinomas. *Am. J. Pathol.,* **2010**, *176*(5), 2435-2446.
http://dx.doi.org/10.2353/ajpath.2010.081059 PMID: 20228225

[73] Bronger, H.; Karge, A.; Dreyer, T.; Zech, D.; Kraeft, S.; Avril, S.; Kiechle, M.; Schmitt, M. Induction of cathepsin B by the CXCR3 chemokines CXCL9 and CXCL10 in human breast cancer cells. *Oncol. Lett.,* **2017**, *13*(6), 4224-4230.
http://dx.doi.org/10.3892/ol.2017.5994
PMID: 28599423

[74] Saahene, R.O.; Wang, J.; Wang, M.L.; Agbo, E.; Song, H. The role of CXC chemokine ligand 4/CXC chemokine receptor 3-B in breast cancer progression. *Biotech. Histochem.,* **2019**, *94*(1), 53-59.
http://dx.doi.org/10.1080/10520295.2018.1497201
PMID: 30264586

[75] Utsumi, T.; Suyama, T.; Imamura, Y.; Fuse, M.; Sakamoto, S.; Nihei, N.; Ueda, T.; Suzuki, H.; Seki, N.; Ichikawa, T. The association of CXCR3 and renal cell carcinoma metastasis. *J. Urol.,* **2014**, *192*(2), 567-574.
http://dx.doi.org/10.1016/j.juro.2014.01.100
PMID: 24518777

[76] Maekawa, S.; Iwasaki, A.; Shirakusa, T.; Kawakami, T.; Yanagisawa, J.; Tanaka, T.; Shibaguchi, H.; Kinugasa, T.; Kuroki, M.; Kuroki, M. Association between the expression of chemokine receptors CCR7 and CXCR3, and lymph node metastatic potential in lung adenocarcinoma. *Oncol. Rep.,* **2008**, *19*(6), 1461-1468.
PMID: 18497951

[77] Zhou, H.; Wu, J.; Wang, T.; Zhang, X.; Liu, D. CXCL10/CXCR3 axis promotes the invasion of gastric cancer *via* PI3K/AKT pathway-dependent MMPs production. *Biomed. Pharmacother.,* **2016**, *82*, 479-488.
http://dx.doi.org/10.1016/j.biopha.2016.04.069
PMID: 27470388

[78] Shaul, M.E.; Fridlender, Z.G. Neutrophils as active regulators of the immune system in the tumor microenvironment. *J. Leukoc. Biol.,* **2017**, *102*(2), 343-349. http://dx.doi.org/10.1189/jlb.5MR1216-508R PMID: 28264904

[79] Xu, X.; Jackson, P.L.; Tanner, S.; Hardison, M.T.; Abdul Roda, M.; Blalock, J.E.; Gaggar, A. A self-propagating matrix metalloprotease-9 (MMP-9) dependent cycle of chronic neutrophilic inflammation. *PLoS One,* **2011**, *6*(1), e15781. http://dx.doi.org/10.1371/journal.pone.0015781 PMID: 21249198

[80] Overbeek, S.A.; Kleinjan, M.; Henricks, P.A.; Kamp, V.M.; Ricciardolo, F.L.; Georgiou, N.A.; Garssen, J.; Kraneveld, A.D.; Folkerts, G. Chemo-attractant N-acetyl proline-glycine-proline induces CD11b/CD18-dependent neutrophil adhesion. *Biochim. Biophys. Acta,* **2013**, *1830*(1), 2188-2193. http://dx.doi.org/10.1016/j.bbagen.2012.09.023 PMID: 23041749

[81] Pfister, R.R.; Haddox, J.L.; Sommers, C.I.; Lam, K.W. Identification and synthesis of chemotactic tripeptides from alkali-degraded whole cornea. A study of N-acetyl-proline-glycine-proline and N-methyl-proline-glycine-proline. *Invest. Ophthalmol. Vis. Sci.,* **1995**, *36*(7), 1306-1316. PMID: 7775108

[82] Pfister, R.R.; Haddox, J.L.; Sommers, C.I. Injection of chemoattractants into normal cornea: a model of inflammation after alkali injury. *Invest. Ophthalmol. Vis. Sci.,* **1998**, *39*(9), 1744-1750. PMID: 9699566

[83] Saintigny, P.; Massarelli, E.; Lin, S.; Ahn, Y.H.; Chen, Y.; Goswami, S.; Erez, B.; O'Reilly, M.S.; Liu, D.; Lee, J.J.; Zhang, L.; Ping, Y.; Behrens, C.; Solis Soto, L.M.; Heymach, J.V.; Kim, E.S.; Herbst, R.S.; Lippman, S.M.; Wistuba, I.I.; Hong, W.K.; Kurie, J.M.; Koo, J.S. CXCR2 expression in tumor cells is a poor prognostic factor and promotes invasion and metastasis in lung adenocarcinoma. *Cancer Res.,* **2013**, *73*(2), 571-582. http://dx.doi.org/10.1158/0008-5472.CAN-12-0263 PMID: 23204236

[84] Nannuru, K.C.; Sharma, B.; Varney, M.L.; Singh, R.K. Role of chemokine receptor CXCR2 expression in mammary tumor growth, angiogenesis and metastasis. *J. Carcinog.,* **2011**, *10*, 40. http://dx.doi.org/10.4103/1477-3163.92308 PMID: 22368515

[85] Taki, M.; Abiko, K.; Baba, T.; Hamanishi, J.; Yamaguchi, K.; Murakami, R.; Yamanoi, K.; Horikawa, N.; Hosoe, Y.; Nakamura, E.; Sugiyama, A.; Mandai, M.; Konishi, I.; Matsumura, N. Snail promotes ovarian cancer progression by recruiting myeloid-derived suppressor cells *via* CXCR2 ligand upregulation. *Nat. Commun.,* **2018**, *9*(1), 1685. http://dx.doi.org/10.1038/s41467-018-03966-7 PMID: 29703902

[86] Bekaert, S.; Fillet, M.; Detry, B.; Pichavant, M.; Marée, R.; Noel, A.; Rocks, N.; Cataldo, D. Inflammation-generated extracellular matrix fragments drive lung metastasis. *Cancer Growth Metastasis,* **2017**, *10,* 1179064417745539. http://dx.doi.org/10.1177/1179064417745539 PMID: 29308014

[87] Samara, G.J.; Lawrence, D.M.; Chiarelli, C.J.; Valentino, M.D.; Lyubsky, S.; Zucker, S.; Vaday, G.G. CXCR4-mediated adhesion and MMP-9 secretion in head and neck squamous cell carcinoma. *Cancer Lett.,* **2004**, *214*(2), 231-241. http://dx.doi.org/10.1016/j.canlet.2004.04.035 PMID: 15363550

[88] Brand, S.; Dambacher, J.; Beigel, F.; Olszak, T.; Diebold, J.; Otte, J.M.; Göke, B.; Eichhorst, S.T. CXCR4 and CXCL12 are inversely expressed in colorectal cancer cells and modulate cancer cell migration, invasion and MMP-9 activation. *Exp. Cell Res.,* **2005**, *310*(1), 117-130. http://dx.doi.org/10.1016/j.yexcr.2005.07.006 PMID: 16125170

[89] Qiao, N.; Wang, L.; Wang, T.; Li, H. Inflammatory CXCL12-CXCR4/CXCR7 axis mediates G-protein signaling pathway to influence the invasion and migration of nasopharyngeal carcinoma cells. *Tumour Biol.,* **2016**, *37*(6), 8169-8179. http://dx.doi.org/10.1007/s13277-015-4686-2 PMID: 26715277

[90] Hao, L.; Zhang, C.; Qiu, Y.; Wang, L.; Luo, Y.; Jin, M.; Zhang, Y.; Guo, T.B.; Matsushima, K.; Zhang, Y. Recombination of CXCR4, VEGF, and MMP-9 predicting lymph node metastasis in human breast cancer. *Cancer Lett.,* **2007**, *253*(1), 34-42. http://dx.doi.org/10.1016/j.canlet.2007.01.005 PMID: 17306924

[91] Iwakura, Y.; Ishigame, H.; Saijo, S.; Nakae, S. Functional specialization of interleukin-17 family members. *Immunity,* **2011**, *34*(2), 149-162. http://dx.doi.org/10.1016/j.immuni.2011.02.012 PMID: 21349428

[92] Iida, T.; Iwahashi, M.; Katsuda, M.; Ishida, K.; Nakamori, M.; Nakamura, M.; Naka, T.; Ojima, T.; Ueda, K.; Hayata, K.; Yasuoka, H.; Yamaue, H. Prognostic significance of IL-17 mRNA expression in peritoneal lavage in gastric cancer patients who underwent curative resection. *Oncol. Rep.,* **2014**, *31*(2), 605-612. http://dx.doi.org/10.3892/or.2013.2911 PMID: 24337702

[93] Fabre, J.; Giustiniani, J.; Garbar, C.; Antonicelli, F.; Merrouche, Y.; Bensussan, A.; Bagot, M.; Al-Dacak, R. Targeting the tumor microenvironment: the protumor effects of IL-17 related to cancer type. *Int. J. Mol. Sci.,* **2016**, *17*(9), 1433. http://dx.doi.org/10.3390/ijms17091433 PMID: 27589729

[94] Liao, R.; Sun, J.; Wu, H.; Yi, Y.; Wang, J.X.; He, H.W.; Cai, X.Y.; Zhou, J.; Cheng, Y.F.; Fan, J.; Qiu,

S.J. High expression of IL-17 and IL-17RE associate with poor prognosis of hepatocellular carcinoma. *J. Exp. Clin. Cancer Res.,* **2013**, *32*, 3. http://dx.doi.org/10.1186/1756-9966-32-3 PMID: 23305119

[95] Parajuli, P.; Anand, R.; Mandalaparty, C.; Suryadevara, R.; Sriranga, P.U.; Michelhaugh, S.K.; Cazacu, S.; Finniss, S.; Thakur, A.; Lum, L.G.; Schalk, D.; Brodie, C.; Mittal, S. Preferential expression of functional IL-17R in glioma stem cells: potential role in self-renewal. *Oncotarget,* **2016**, *7*(5), 6121-6135. http://dx.doi.org/10.18632/oncotarget.6847 PMID: 26755664

[96] Bie, Q.L.; Sun, C.X.; Gong, A.H.; Li, C.Y.; Su, Z.L.; Zheng, D.; Ji, X.Y.; Wu, Y.M.; Guo, Q.; Wang, S.; Xu, H. Non-tumor tissue derived interleukin-17 B activates IL-17RB/AKT/beta-catenin pathway to enhance the stemness of gastric cancer. *Sci. Rep. U.K.,* **2016**, *6*, 25447.

[97] Wu, H.H.; Hwang-Verslues, W.W.; Lee, W.H.; Huang, C.K.; Wei, P.C.; Chen, C.L.; Shew, J.Y.; Lee, E.Y.; Jeng, Y.M.; Tien, Y.W.; Ma, C.; Lee, W.H. Targeting IL-17B-IL-17RB signaling with an anti-IL-17RB antibody blocks pancreatic cancer metastasis by silencing multiple chemokines. *J. Exp. Med.,* **2015**, *212*(3), 333-349. http://dx.doi.org/10.1084/jem.20141702 PMID: 25732306

[98] Eiro, N.; Fernandez-Gomez, J.; Sacristán, R.; Fernandez-Garcia, B.; Lobo, B.; Gonzalez-Suarez, J.; Quintas, A.; Escaf, S.; Vizoso, F.J. Stromal factors involved in human prostate cancer development, progression and castration resistance. *J. Cancer Res. Clin. Oncol.,* **2017**, *143*(2), 351-359. http://dx.doi.org/10.1007/s00432-016-2284-3 PMID: 27787597

[99] Ren, L.; Xu, Y.; Liu, C.; Wang, S.; Qin, G. IL-17RB enhances thyroid cancer cell invasion and metastasis *via* ERK1/2 pathway-mediated MMP-9 expression. *Mol. Immunol.,* **2017**, *90*, 126-135. http://dx.doi.org/10.1016/j.molimm.2017.06.034 PMID: 28715683

[100] Liu, D.; Zhang, R.; Wu, J.; Pu, Y.; Yin, X.; Cheng, Y.; Wu, J.; Feng, C.; Luo, Y.; Zhang, J. Interleukin-17A promotes esophageal adenocarcinoma cell invasiveness through ROS-dependent, NF-κB-mediated MMP-2/9 activation. *Oncol. Rep.,* **2017**, *37*(3), 1779-1785. http://dx.doi.org/10.3892/or.2017.5426 PMID: 28184939

[101] Apte, R.N.; Dotan, S.; Elkabets, M.; White, M.R.; Reich, E.; Carmi, Y.; Song, X.; Dvozkin, T.; Krelin, Y.; Voronov, E. The involvement of IL-1 in tumorigenesis, tumor invasiveness, metastasis and tumor-host interactions. *Cancer Metastasis Rev.,* **2006**, *25*(3), 387-408. http://dx.doi.org/10.1007/s10555-006-9004-4 PMID: 17043764

[102] Xu, D.; Matsuo, Y.; Ma, J.; Koide, S.; Ochi, N.; Yasuda, A.; Funahashi, H.; Okada, Y.; Takeyama, H. Cancer cell-derived IL-1α promotes HGF secretion by stromal cells and enhances metastatic potential in pancreatic cancer cells. *J. Surg. Oncol.,* **2010**, *102*(5), 469-477. http://dx.doi.org/10.1002/jso.21530 PMID: 20872950

[103] Tjomsland, V.; Pomianowska, E.; Aasrum, M.; Sandnes, D.; Verbeke, C.S.; Gladhaug, I.P. Profile of MMP and TIMP expression in human pancreatic stellate cells: regulation by IL-1α and TGFβ and implications for migration of pancreatic cancer cells. *Neoplasia,* **2016**, *18*(7), 447-456. http://dx.doi.org/10.1016/j.neo.2016.06.003 PMID: 27435927

[104] Apte, M.V.; Wilson, J.S.; Lugea, A.; Pandol, S.J. A starring role for stellate cells in the pancreatic cancer microenvironment. *Gastroenterology,* **2013**, *144*(6), 1210-1219. http://dx.doi.org/10.1053/j.gastro.2012.11.037 PMID: 23622130

[105] Adachi, T.; Alam, R. The mechanism of IL-5 signal transduction. *Am. J. Physiol.,* **1998**, *275*(3), C623-C633. http://dx.doi.org/10.1152/ajpcell.1998.275.3.C623 PMID: 9730944

[106] Takatsu, K.; Nakajima, H. IL-5 and eosinophilia. *Curr. Opin. Immunol.,* **2008**, *20*(3), 288-294. http://dx.doi.org/10.1016/j.coi.2008.04.001 PMID: 18511250

[107] Sato, S.; Katagiri, T.; Takaki, S.; Kikuchi, Y.; Hitoshi, Y.; Yonehara, S.; Tsukada, S.; Kitamura, D.; Watanabe, T.; Witte, O.; Takatsu, K. IL-5 receptor-mediated tyrosine phosphorylation of SH2/SH3-containing proteins and activation of Bruton's tyrosine and Janus 2 kinases. *J. Exp. Med.,* **1994**, *180*(6), 2101-2111. http://dx.doi.org/10.1084/jem.180.6.2101 PMID: 7525847

[108] Lee, E.J.; Lee, S.J.; Kim, S.; Cho, S.C.; Choi, Y.H.; Kim, W.J.; Moon, S.K. Interleukin-5 enhances the migration and invasion of bladder cancer cells *via* ERK1/2-mediated MMP-9/NF-κB/AP-1 pathway: involvement of the p21WAF1 expression. *Cell. Signal.,* **2013**, *25*(10), 2025-2038. http://dx.doi.org/10.1016/j.cellsig.2013.06.004 PMID: 23770289

[109] Park, S.L.; Kim, W.J.; Moon, S.K. p21WAF1 mediates the IL-15-induced migration and invasion of human bladder cancer 5637 cells *via* the ERK1/2/NF-κB/MMP-9 pathway. *Int. Immunopharmacol.,* **2014**, *22*(1), 59-65. http://dx.doi.org/10.1016/j.intimp.2014.06.008 PMID: 24953855

[110] Ghosh, P.; Mitra, D.; Mitra, S.; Ray, S.; Banerjee, S.; Murmu, N. *Madhuca indica* inhibits breast cancer cell proliferation by modulating COX-2 expression. *Curr. Mol. Med.,* **2018**, *18*(7), 459-474.

http://dx.doi.org/10.2174/1566524019666181212100808 PMID: 30539699

[111] Ren, J.; Liu, J.; Sui, X. Correlation of COX-2 and MMP-13 expressions with gastric cancer and their effects on prognosis. *J. BUON,* **2018**, *23*(3), 665-671. PMID: 30003735

[112] Tang, H.; Liu, Y.; Wang, C.; Zheng, H.; Chen, Y.; Liu, W.; Chen, X.; Zhang, J.; Chen, H.; Yang, Y.; Yang, J. Inhibition of COX-2 and EGFR by Melafolone improves Anti-PD-1 therapy through vascular normalization and PD-L1 downregulation in lung cancer. *J. Pharmacol. Exp. Ther.,* **2019**, *368*(3), 401-413. http://dx.doi.org/10.1124/jpet.118.254359 PMID: 30591531

[113] Li, T.J.; Cui, J. COX-2, MMP-7 expression in oral lichen planus and oral squamous cell carcinoma. *Asian Pac. J. Trop. Med.,* **2013**, *6*(8), 640-643. http://dx.doi.org/10.1016/S1995-7645(13)60110-8 PMID: 23790336

[114] Lopez-Gonzalez, J.S.; Avila-Moreno, F.; Prado-Garcia, H.; Aguilar-Cazares, D.; Mandoki, J.J.; Meneses-Flores, M. Lung carcinomas decrease the number of monocytes/macrophages (CD14+ cells) that produce TNF-alpha. *Clin. Immunol.,* **2007**, *122*(3), 323-329. http://dx.doi.org/10.1016/j.clim.2006.11.003 PMID: 17175197

[115] Hagemann, T.; Biswas, S.K.; Lawrence, T.; Sica, A.; Lewis, C.E. Regulation of macrophage function in tumors: the multifaceted role of NF-kappaB. *Blood,* **2009**, *113*(14), 3139-3146. http://dx.doi.org/10.1182/blood-2008-12-172825 PMID: 19171876

[116] Wang, X.; Zhao, X.; Wang, K.; Wu, L.; Duan, T. Interaction of monocytes/macrophages with ovarian cancer cells promotes angiogenesis *in vitro*. *Cancer Sci.,* **2013**, *104*(4), 516-523. http://dx.doi.org/10.1111/cas.12110 PMID: 23347208

[117] Ke, X.; Zhang, S.; Wu, M.; Lou, J.; Zhang, J.; Xu, T.; Huang, L.; Huang, P.; Wang, F.; Pan, S. Tumor-associated macrophages promote invasion *via* Toll-like receptors signaling in patients with ovarian cancer. *Int. Immunopharmacol.,* **2016**, *40*, 184-195. http://dx.doi.org/10.1016/j.intimp.2016.08.029 PMID: 27608303

[118] Rao, A.; Luo, C.; Hogan, P.G. Transcription factors of the NFAT family: regulation and function. *Annu. Rev. Immunol.,* **1997**, *15*, 707-747. http://dx.doi.org/10.1146/annurev.immunol.15.1.707 PMID: 9143705

[119] Chen, L.; Rao, A.; Harrison, S.C. Signal integration by transcription-factor assemblies: interactions of NF-AT1 and AP-1 on the IL-2 promoter. *Cold Spring Harb. Symp. Quant. Biol.,* **1999**, *64*, 527-531. http://dx.doi.org/10.1101/sqb.1999.64.527 PMID: 11232329

[120] Macian, F. NFAT proteins: key regulators of T-cell development and function. *Nat. Rev. Immunol.,* **2005**, *5*(6), 472-484. http://dx.doi.org/10.1038/nri1632 PMID: 15928679

[121] Lee, J.U.; Kim, L.K.; Choi, J.M. Revisiting the concept of targeting NFAT to control T cell immunity and autoimmune diseases. *Front. Immunol.,* **2018**, *9*, 2747. http://dx.doi.org/10.3389/fimmu.2018.02747 PMID: 30538703

[122] Werneck, M.B.; Vieira-de-Abreu, A.; Chammas, R.; Viola, J.P. NFAT1 transcription factor is central in the regulation of tissue microenvironment for tumor metastasis. *Cancer Immunol. Immunother.,* **2011**, *60*(4), 537-546. http://dx.doi.org/10.1007/s00262-010-0964-4 PMID: 21225259

[123] Pan, M.G.; Xiong, Y.; Chen, F. NFAT gene family in inflammation and cancer. *Curr. Mol. Med.,* **2013**, *13*(4), 543-554. http://dx.doi.org/10.2174/1566524011313040007 PMID: 22950383

[124] Qin, J.J.; Nag, S.; Wang, W.; Zhou, J.; Zhang, W.D.; Wang, H.; Zhang, R. NFAT as cancer target: mission possible? *Biochim. Biophys. Acta,* **2014**, *1846*(2), 297-311. PMID: 25072963

[125] Quang, C.T.; Leboucher, S.; Passaro, D.; Fuhrmann, L.; Nourieh, M.; Vincent-Salomon, A.; Ghysdael, J. The calcineurin/NFAT pathway is activated in diagnostic breast cancer cases and is essential to survival and metastasis of mammary cancer cells. *Cell Death Dis.,* **2015**, *6,* e1658. http://dx.doi.org/10.1038/cddis.2015.14 PMID: 25719243

[126] Qin, J.J.; Wang, W.; Voruganti, S.; Wang, H.; Zhang, W.D.; Zhang, R. Inhibiting NFAT1 for breast cancer therapy: new insights into the mechanism of action of MDM2 inhibitor JapA. *Oncotarget,* **2015**, *6*(32), 33106-33119. http://dx.doi.org/10.18632/oncotarget.5851 PMID: 26461225

[127] Braeuer, R.R.; Zigler, M.; Kamiya, T.; Dobroff, A.S.; Huang, L.; Choi, W.; McConkey, D.J.; Shoshan, E.; Mobley, A.K.; Song, R.; Raz, A.; Bar-Eli, M. Galectin-3 contributes to melanoma growth and metastasis *via* regulation of NFAT1 and autotaxin. *Cancer Res.,* **2012**, *72*(22), 5757-5766. http://dx.doi.org/10.1158/0008-5472.CAN-12-2424 PMID: 22986745

[128] Shoshan, E.; Braeuer, R.R.; Kamiya, T.; Mobley, A.K.; Huang, L.; Vasquez, M.E.; Velazquez-Torres, G.; Chakravarti, N.; Ivan, C.; Prieto, V.; Villares, G.J.; Bar-Eli, M. NFAT1 directly regulates IL-8 and MMP-3 to promote melanoma tumor growth and metastasis. *Cancer Res.,* **2016**, *76*(11), 3145-3155. http://dx.doi.org/10.1158/0008-5472.CAN-15-2511 PMID: 27013197

[129] Liu, J.F.; Zhao, S.H.; Wu, S.S. Depleting NFAT1 expression inhibits the ability of invasion and migration of human lung cancer cells. *Cancer Cell Int.,* **2013**, *13*(1), 41. http://dx.doi.org/10.1186/1475-2867-13-41 PMID: 23663403

[130] Vázquez-Cedeira, M.; Lazo, P.A. Human VRK2 (vaccinia-related kinase 2) modulates tumor cell invasion by hyperactivation of NFAT1 and expression of cyclooxygenase-2. *J. Biol. Chem.,* **2012**, *287*(51), 42739-42750. http://dx.doi.org/10.1074/jbc.M112.404285 PMID: 23105117

[131] Chen, P.; Shan, Z.; Zhao, J.; Li, F.; Zhang, W.; Yang, L.; Huang, Z. NFAT1 promotes cell motility through MMP-3 in esophageal squamous cell carcinoma. *Biomed. Pharmacother.,* **2017**, *86*, 541-546. http://dx.doi.org/10.1016/j.biopha.2016.12.050 PMID: 28024290

[132] Kollias, G.; Douni, E.; Kassiotis, G.; Kontoyiannis, D. The function of tumour necrosis factor and receptors in models of multi-organ inflammation, rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease. *Ann. Rheum. Dis.,* **1999**, *58*(Suppl. 1), 132-139. http://dx.doi.org/10.1136/ard.58.2008.i32 PMID: 10577971

[133] Black, R.A.; Rauch, C.T.; Kozlosky, C.J.; Peschon, J.J.; Slack, J.L.; Wolfson, M.F.; Castner, B.J.; Stocking, K.L.; Reddy, P.; Srinivasan, S.; Nelson, N.; Boiani, N.; Schooley, K.A.; Gerhart, M.; Davis, R.; Fitzner, J.N.; Johnson, R.S.; Paxton, R.J.; March, C.J.; Cerretti, D.P. A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cells. *Nature,* **1997**, *385*(6618), 729-733. http://dx.doi.org/10.1038/385729a0 PMID: 9034190

[134] Moss, M.L.; Jin, S.L.; Milla, M.E.; Bickett, D.M.; Burkhart, W.; Carter, H.L.; Chen, W.J.; Clay, W.C.; Didsbury, J.R.; Hassler, D.; Hoffman, C.R.; Kost, T.A.; Lambert, M.H.; Leesnitzer, M.A.; McCauley, P.; McGeehan, G.; Mitchell, J.; Moyer, M.; Pahel, G.; Rocque, W.; Overton, L.K.; Schoenen, F.; Seaton, T.; Su, J.L.; Becherer, J.D. Cloning of a disintegrin metalloproteinase that processes precursor tumour-necrosis factor-alpha. *Nature,* **1997**, *385*(6618), 733-736. http://dx.doi.org/10.1038/385733a0 PMID: 9034191

[135] Arcone, R.; Palma, M.; Pagliara, V.; Graziani, G.; Masullo, M.; Nardone, G. Green tea polyphenols affect invasiveness of human gastric MKN-28 cells by inhibition of LPS or TNF-α induced Matrix Metalloproteinase-9/2. *Biochim Open,* **2016**, *3*, 56-63. http://dx.doi.org/10.1016/j.biopen.2016.10.002 PMID: 29450132

[136] Jung, Y.S.; Lee, S.O. Apomorphine suppresses TNF-α-induced MMP-9 expression and cell invasion through inhibition of ERK/AP-1 signaling pathway in MCF-7 cells. *Biochem. Biophys. Res. Commun.,* **2017**, *487*(4), 903-909. http://dx.doi.org/10.1016/j.bbrc.2017.04.151 PMID: 28465234

[137] Lee, S.J.; Park, S.S.; Lee, U.S.; Kim, W.J.; Moon, S.K. Signaling pathway for TNF-α-induced MMP-9 expression: mediation through p38 MAP kinase, and inhibition by anti-cancer molecule magnolol in human urinary bladder cancer 5637 cells. *Int. Immunopharmacol.,* **2008**, *8*(13-14), 1821-1826. http://dx.doi.org/10.1016/j.intimp.2008.08.018 PMID: 18801463

[138] García, M.A.; Gil, J.; Ventoso, I.; Guerra, S.; Domingo, E.; Rivas, C.; Esteban, M. Impact of protein kinase PKR in cell biology: from antiviral to antiproliferative action. *Microbiol. Mol. Biol. Rev.,* **2006**, *70*(4), 1032-1060. http://dx.doi.org/10.1128/MMBR.00027-06 PMID: 17158706

[139] Gilbert, S.J.; Duance, V.C.; Mason, D.J. Does protein kinase R mediate TNF-alpha- and ceramide-induced increases in expression and activation of matrix metalloproteinases in articular cartilage by a novel mechanism? *Arthritis Res. Ther.,* **2004**, *6*(1), R46-R55. http://dx.doi.org/10.1186/ar1024 PMID: 14979937

[140] Ma, C.H.; Wu, C.H.; Jou, I.M.; Tu, Y.K.; Hung, C.H.; Hsieh, P.L.; Tsai, K.L. PKR activation causes inflammation and MMP-13 secretion in human degenerated articular chondrocytes. *Redox Biol.,* **2018**, *14*, 72-81. http://dx.doi.org/10.1016/j.redox.2017.08.011 PMID: 28869834

[141] Huang, H.; Wu, K.; Ma, J.; Du, Y.; Cao, C.; Nie, Y. Dopamine D2 receptor suppresses gastric cancer cell invasion and migration *via* inhibition of EGFR/AKT/MMP-13 pathway. *Int. Immunopharmacol.,* **2016**, *39*, 113-120. http://dx.doi.org/10.1016/j.intimp.2016.07.002 PMID: 27468100

[142] Wu, Z.; Yin, H.; Liu, T.; Yan, W.; Li, Z.; Chen, J.; Chen, H.; Wang, T.; Jiang, Z.; Zhou, W.; Xiao, J. MiR-126-5p regulates osteoclast differentiation and bone resorption in giant cell tumor through inhibition of MMP-13. *Biochem. Biophys. Res. Commun.,* **2014**, *443*(3), 944-949. http://dx.doi.org/10.1016/j.bbrc.2013.12.075 PMID: 24360951

[143] Zhou, Y.; Hu, Z.; Li, N.; Jiang, R. Interleukin-32 stimulates osteosarcoma cell invasion and motility *via* AKT pathway-mediated MMP-13 expression. *Int. J. Mol. Med.,* **2015**, *35*(6), 1729-1733. http://dx.doi.org/10.3892/ijmm.2015.2159 PMID: 25846944

[144] Phienwej, H.; Swasdichira, I.S.; Amnuoypol, S.; Pavasant, P.; Sumrejkanchanakij, P. Tinospora crispa extract inhibits MMP-13 and migration of head and neck squamous cell carcinoma cell lines. *Asian Pac. J. Trop. Biomed.,* **2015**, *5*(9), 738-743. http://dx.doi.org/10.1016/j.apjtb.2015.07.001

[145] Eba, H.; Murasawa, Y.; Iohara, K.; Isogai, Z.; Nakamura, H.; Nakamura, H.; Nakashima, M. The anti-

inflammatory effects of matrix metalloproteinase-3 on irreversible pulpitis of mature erupted teeth. *PLoS One,* **2012**, *7*(12), e52523.
http://dx.doi.org/10.1371/journal.pone.0052523
PMID: 23285075

[146] McMillan, S.J.; Kearley, J.; Campbell, J.D.; Zhu, X.W.; Larbi, K.Y.; Shipley, J.M.; Senior, R.M.; Nourshargh, S.; Lloyd, C.M. Matrix metalloproteinase-9 deficiency results in enhanced allergen-induced airway inflammation. *J. Immunol.,* **2004**, *172*(4), 2586-2594.
http://dx.doi.org/10.4049/jimmunol.172.4.2586
PMID: 14764732

[147] Brauer, R.; Tureckova, J.; Kanchev, I.; Khoylou, M.; Skarda, J.; Prochazka, J.; Spoutil, F.; Beck, I.M.; Zbodakova, O.; Kasparek, P.; Korinek, V.; Chalupsky, K.; Karhu, T.; Herzig, K.H.; Hajduch, M.; Gregor, M.; Sedlacek, R. MMP-19 deficiency causes aggravation of colitis due to defects in innate immune cell function. *Mucosal Immunol.,* **2016**, *9*(4), 974-985.
http://dx.doi.org/10.1038/mi.2015.117
PMID: 26555704

[148] McMahan, R.S.; Birkland, T.P.; Smigiel, K.S.; Vandivort, T.C.; Rohani, M.G.; Manicone, A.M.; McGuire, J.K.; Gharib, S.A.; Parks, W.C. Stromelysin-2 (MMP10) moderates inflammation by controlling macrophage activation. *J. Immunol.,* **2016**, *197*(3), 899-909.
http://dx.doi.org/10.4049/jimmunol.1600502 PMID: 27316687