Specific signaling pathways and drugs play key role in regulation of angiogenesis

Sanaz Kavoosi [1], Mehdi Ahmadifar[2], Tina Mandegar Fard [3], Negar Safar Lavasani [3], Arsalan Jalili [2,4,*], Amin Ebrahimi Sadrabadi [2,5,*]

[1]Department of Biology, Central Tehran Branch, Islamic Azad University, Tehran, Iran
[2]Department of Stem Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACER, Tehran, Iran
[3]Department of Biology, Collage of Science, University of Science and Culture, ACER, Tehran Branch, Iran
[4]Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Cancer Biomedical Research Center, Tehran, Iran

***Corresponding authors:**. Arsalan Jalili, Amin Ebrahimi Sadrabadi. Department of Stem Cells and Developmental Biology at Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran. E-mail: Jalili.arsalan@royaninstitute.org; Amin.ebrahimi@royaninstitute.org*

ABSTRACT

In this study, angiogenesis inducers and inhibitors and some important drugs are introduced. Abnormal angiogenesis can occur if the balance between inhibitory and inducible factors disappears. Angiogenesis inducers include EGF, FGF2, TGF-β, VEGF, G-CSF, HGF, TGF-α, IL-8, TNF-α and angiogenesis inhibitors such as endostatin, interleukin, prolactin, interferons, IL-1, IL-12, angiostatin, and IL-18. On the other hand, many drugs can affect these signaling pathways.

Keywords: Signaling pathway, angiogenesis, cancer regulation, inducers

INTRODUCTION

Angiogenesis is one of the stages of cancer progression in which endothelial cells begin to proliferate [1]. To initiate angiogenesis, angiogenesis inducers bind to endothelial cell surface receptors and activate endothelial cells. As a result of this activation, the matrix metalloprotease is released and damages the capillary basement membrane. The activated

endothelial cells then migrate and expand outside the main blood vessel [2]. Angiogenesis itself is divided into two types: physiological angiogenesis and pathological angiogenesis, each with its own characteristics and effects. In general, angiogenesis involves a series of cytokines that any alteration that causes these cytokines to become out of balance can cause abnormal angiogenesis [3]. The cytokines involved in their angiogenesis are divided into two groups: angiogenesis inhibitors and inducers. Angiogenesis-inducing factors include VEGF, BFGF, TNF-α, G-CSF, PDGF, PGF, TGF-β, TGF-α, IL-8, HGF and EGF [4] (Table 1). Each of these cytokines have their own specificity and function through different signaling pathways that can eventually stimulate cell proliferation and induce angiogenesis. The other group are cytokines that inhibit angiogenesis, including prolactin, endostatin, angiotensin, interferons, IL-12, IL-1 [4], IL-18 [5] (Table 2). They disrupt the formation of new vessels and eliminate the blood vessels that are formed. Changes in balance toward angiogenesis inhibition can impair important physiological roles, such as wound healing and fetal growth [5]. The angiogenesis inhibitors, each with its own specificity and function, can function through different signaling pathways that eventually lead to

angiogenesis inhibition, inhibition of proliferation and induction of apoptosis. The purpose of this article is to investigate the common pathways between cytokines involved in angiogenesis and are presented in Tables 1 and 2 for a complete description of these factors. Each of these factors acts through one or more signaling pathways, and this study identifies a number of drugs that may affect these signaling pathways.

Importance of investigating the signaling pathways and drugs that affect these pathways

Signaling pathways are important means of linking intracellular segments and interacting extracellular segments with intracellular junctions that play essential role in various cellular processes. An oncogenic mutation or abnormal expression in any of the components of the signaling pathway can impair the function of the signaling pathways [6]. One of these is the MAPK/ERK signaling pathway, which involves a chain of proteins in the cell. When the ligand binds to the receptor at the cell surface [7], cellular proliferation is activated and can induce cell differentiation and proliferation as well as apoptosis in eukaryotic cells. Different cytokines act through this signaling pathway and several of them are mentioned in this article [8] (Table 1). Various drugs can affect this pathway. Dihydroartemisinin (DHA) is a

8

derivative of artemisinin that has anti-angiogenic activity. Stopping tumor angiogenesis can be an important treatment for cancer. A study of the effect of DHA on human umbilical vein cells (HUVECS) has shown that DHA can decrease ERK1/2 phosphorylation and decrease mRNA regulation, causing ERK1/2 protein expression in HUVECS [9] and induction of apoptosis through activation of p38 MAPK [10] and also suppresses transcription and also affects the c-MYC and c-FOS factors [9]. NF-KB is another signaling pathway found in all animal species and responds to stimuli such as cytokines, stress, free radicals, and so on. NF-KB plays a role in modulating cellular processes and, if out of order, can cause autoimmune diseases, inflammation and viral infections, and so on. This signaling pathway can be involved in the induction and inhibition of angiogenesis [11,12]. Various drugs can affect this pathway. For example: metformin is the first common drug to treat type 2 diabetes. A study investigating the effect of metformin on the up-regulation of IL-8 by Lithochalic acid (LCA) in HCT116 Colorectal Cancer (CRC) cells showed that Reactive Oxygen Species (ROS) induce IL-8 regulation. Induction of LCA, which is activated by NF-KB transcription factor, plays an important role in stimulating metformin by inhibiting ROS production and by LCA, eventually leads to NF-KB signaling and NF-KB is essential for IL-8 up-regulation [13]. Ginsenoside Rk1 is another drug that can affect the NF-KB signaling pathway. Ginsenoside rk1 is a natural drug product that induces apoptosis by inhibiting NF-KB transcription in lung endocarcinoma cells and disrupts the cell cycle at G1 stage and acts as an antitumor modulator. RK1 can increase the expression of BAX, PARP and cleavage protein in caspase 3 and 9, decrease BCL2 expression, induce an increase in PD-L1 expression by inhibiting NF-KB signaling [14,15]. AKT is another signaling pathway that kinases of this signaling pathway are involved in a variety of processes including cell proliferation, cell survival, invasion response and angiogenesis. AKT is a cell survival factor and has anti-apoptotic activity that is involved in metabolic regulation and cell signaling [16]. Various cytokines work through this pathway, some of which are listed in Table 1.

9

Table 1.| List of angiogenesis inducing factors along with structural features, secretion source, signaling pathways, and function

Angiogenesis inducing factors	Full name	Structural features	Source	Function	Signaling pathways
EGF	Epidermal growth factor	It has 53 amino acids and has three intramolecular disulfide bonds and a molecular weight KDA6 [28].	Platelets, macrophages, fibroblasts [27]	It is involved in regulating cell growth. It directly promotes epidermal cell proliferation. A nitrogen and oxygen reactive antagonist mediated by keratinocytes. It leads to cell division and induction of angiogenesis [27].	ERK/MAPK [26]
FGF2/bFGF	Fibroblast growth factor	It has 155 amino acids and thus produces 18 kDa protein [34].	Keratinocytes, mast cells, fibroblasts, endothelial cells, smooth muscle cells, chondrocytes [30], [31, 33] [29]	It has a broad role in cell survival and mitogenesis [30]. Involved in a variety of physiological processes including: embryonic development, cell growth, morphogenesis, tissue repellency, tumor growth, invasion and play an important role in angiogenesis [31]. Recent evidence suggests that low levels of this inducer play an important role in the expression of anxiety [32].	MAPK signaling pathway [29]

TGF-β	Transforming growth factor beta	TGFβ1/390 TGFβ2/412 TGFβ3/412 [3,9]	Platelets, keratinocytes, macrophages, lymphocytes, fibroblasts [36]	It activates different substrates and regulatory proteins and transcription of different target genes that are involved in cell differentiation, chemotaxis, proliferation and activation of many TGFβ immune cells [36, 37]. A cytokine regulates three isoforms and regulates many cellular functions including: cell proliferation, differentiation, adhesion, and migration. Increased expression of TGFβ is often associated with malignancy in many cancers and defects in cell growth inhibition response [38].	SMAD [35]
VEGF	Vascular endothelial growth factor	Binding via the transmembrane short helix to a second cytoplasmic catalyst [41]	Platelets [42], neutrophils, macrophages [43], endothelial cells, smooth muscle cells, fibroblasts keratinocytes [44]	Mitogen is specific for endothelial cells [40] . It induces proliferation and migration of endothelial cells and prevents apoptosis. In vivo it causes angiogenesis and plays an important role in the regulation of blood vessels in the blood [41].	PLC-PKC-MAPK [39]

G-CSF	Granulocyte macrophage colony stimulating factor	174-177 aa long protein 19,600 grams per mole [45]	Endothelium, macrophages and a number of other immune cells [45] .	Glycol is a protein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. It is a cytokine and a hormone produced by different tissues that stimulates survival, cell proliferation, differentiation, and stimulates neutrophil progressive function, resulting in the maturation of neutrophils [45].	JAK/STAT, Ras/MAPK, PI3K/AKT [45]
TNF-α	Tumor necrosis factor	233aa ,17kda [50, 51]	Macrophages, natural killer cell lymphocytes, neutrophils, mast cells [49], eosinophils, neurons	The regulation of immune cells is one of the most important mediators of inflammation. One of the cytokines involved in triggering the acute phase reaction in the human body. It is involved in the development of fever, septic shock, cachexia, and tumor progression. [48]	NF-KB, [46]MAPK [47]

12

PGF	Placenta growth factor	A member of the VEGT family. VEGF has a second domain that binds to a second cytoplasmic catalytic domain via short transmembrane helix [41].	In many tissues including trophoblasts [53]and organs such as the heart, thyroid, skeletal muscle, and lung are expressed at low levels [39,52] .	Its main source is during pregnancy. It is a coding gene and is a member of vascular endothelial growth factors VEGF and is strongly associated with angiogenesis [39, 52]. It is involved in trophoblast growth. The proper development of blood vessels in the placenta is crucial for fetal development [53]	PLC/PKC/MAPK [39]
HGF	Hepatocyte growth factor or scatter factor	It is cleaved by serine proteases into the alpha chain of 69 kDa and 34 kDa beta [54]	Mesenchymal cells [56]	Molecularly potent mitogen is a clone. It is involved in stimulating cell growth and inducing multicellular structure. It acts as a liver agent for regeneration [56].	Tyrosine kinase signaling [54,55]
IL-8	Interlukin-8	As a precursor peptide, it is made of 99 amino acids, which then cleave and generate several active IL-8 isoforms. A major peptide form contains 72 amino acids that are secreted by macrophages [59]	Macrophages and cells such as epithelial cells, airway smooth muscle cells [62]and endothelial cells [60]	It is known as a neutrophil chemotactic factor. It has two main functions, causing chemotaxis in the target cells and also migrating to the site of infection. They are monomeric and homodimer and are potent inducers of CXCR2 and CXCR1 receptors. [59-61]	NF-KB , [57] Ribosomal proteins 6 phosphorylation (RPS6) [58]

13

TGF-α	Transforming growth factor alpha	(160aa human) and consists of a second extracellular domain containing a second hydrophobic transmembrane, 50 TGF-α amino acid and a 35-residue long cytoplasmic amino acid [64]	Macrophages, brain cells, keratinocytes [65]	It plays a role in cell proliferation, wound healing, embryogenesis and angiogenesis enhancement. Stimulates proliferation of nerve cells in the damaged brain of adults [64, 65]	MAPK/JNK [63]

One of the drugs that work on this pathway is Aloperine. Aloperine is a potential chemotherapeutic agent for Hepatocellular carcinoma (HCC) that inhibits proliferation in HEP3B and Huh7 cells, by blocking the cell cycle at the G2/M stage and inducing apoptosis by inhibiting PI3K/AKT signaling pathway in HCC cells. Inhibition of this signaling pathway is mediated by decreased expression of P110 α, P85, AKT and PAKT [17]. JNK signaling pathway plays a key role in cell proliferation, survival and cancer cell apoptosis. JNK increases with NF-KB, JAK-STAT, and other signaling pathways, and can eventually lead to cell survival [18]. Different cytokines can function through this pathway. Some of them are listed in Table 2. JNK is one of several ROS pathways where ROS can regulate the AKT/mTOR signaling pathway. ROS is an important pathway for cell survival, cell differentiation, regulation of angiogenesis, and apoptosis [19,20]. One of the drugs that can affect this pathway is erianin, which has anti-tumor and anti-angiogenic effects. Treatment of HaCat cells with erianin inhibits cell proliferation, induction of ROS apoptosis as well as induction of the C-JUN/C-JNK signaling pathway and suppression of the AKT / B protein kinase pathway, but treatment with N-Acetylcysteine (NAC) reverses these effects. Erianin inhibits growth by inducing angiogenesis and inhibiting the cell cycle in the T47D cell line in breast cancer [21]. JAK-STAT is another signaling pathway that is a global intracellular signal transduction pathway and is involved in different processes such as cell proliferation, cell differentiation, apoptosis and immune regulation. JAK-STAT is a relatively simple

signaling pathway. However, the biological consequences of this pathway are complex due to crosstalk with other signaling pathways [22]. Many drugs affect this pathway. One of these drugs is JQ1. JQ1 inhibits cell proliferation and induces apoptosis in ovarian cancer cells. C-MYC has been overexpressed in ovarian cancer, which can itself be considered a therapeutic target [23]. JQ1 makes ovarian cancer cells sensitive to cisplatin, a common drug for chemotherapy in ovarian cancer [24]. JQ1 inhibits cell proliferation and induces apoptosis by targeting C-MYC and BRD4 cells in ovarian cancer [25] and interacts with the JAK-STAT signaling pathway [24].

Angiogenesis

Angiogenesis begins by binding of angiogenesis-inducing factors to their receptor on the endothelial cell surface and activate those endothelial cells and releases the matrix metalloprotease, then destroys the capillary basement membrane and let the activated endothelial cells to migrat. The endothelial cells expand outside the main blood vessel and then attach to the lumen or loop, eventually activating pericytes to stabilize newly formed capillaries [2]. Angiogenesis itself is divided into two types: physiological angiogenesis and pathological angiogenesis, which physiological one play

important role in vessel formation, puberty, vessel remodeling and vessel destruction, on the other hand the pathological angiogenesis plays in tumor events, different ischemic diseases and inflammation. In the process of angiogenesis, a number of related cytokines are involved, which may result in abnormal angiogenesis if the expression of these factors is not sufficient or excessive [3]. Angiogenesis is controlled by the balance between the angiogenesis inducer and the angiogenesis inhibitor. Angiogenesis-inducing factors include EGF, HGF, IL-8, TGFβ, TGFα, PGF, PDGF, G-CSF, TNFα, bFGF and VEGF [4] (Table 1) and are produced by different cell types including: Endothelial cells, smooth muscle cells, platelets, inflammatory cells and cancer cells [66]. In a growing cancer, continuous production of angiogenesis inducers increase the endothelial cell activity and decreases as well as anti-angiogenic factors. One of the most important and potent inducers of angiogenesis is VEGF and bFGF [4], which include VEGF: VEGF-A, VEGF-B, VEGF-C, VEGF-E, VEGF-F and VEGF-D; and VEGF-A has six isoforms under the influence of alternative splicing: VEGF-A183, VEGF-A165, VEGF-A145, VEGF-A121, VEGF-A206, VEGF-A189 and has three receptors, including: VEGFR1, VEGFR2, VEGFR3, which VEGFR1 has the

15

highest affinity for VEGF and PIGF [67]. TGFβ and PDGF are other angiogenic factors that are important for the stabilization of new blood vessels, while TGFβ is responsible for the production of extracellular matrix and the proper interface between ECs and mural cells [66]. and PVHL, a negative regulator of HIF-1 expression, which HIF-1 itself, induces tumor cell creation and secretion of angiogenesis-related factors, as well as increased CXCR4 expression, which contributes to CXCR4 mRNA stability. This study demonstrates that HIF-1 plays an important role in tumor formation, invasion and metastasis [3]. ANG-1 and the endothelial specific tyrosine kinase receptor Tie-2 are one of the most important regulators of angiogenesis and inflammation, and they both play important roles in fetal vascular excretion. Angiopoietin-1 (ANG-1) inhibits apoptosis, increases migration, decreases permeability, stimulates vascular division, heals wounds, and increases lymphatic fluid. Tie-2 initiates cell signaling by stimulating phosphorylation of key tyrosine. Tie-2 is abundant in all endothelial cells that express the ANG/Tie-2 axis through several intracellular pathways including: JNK, P38ERK1/2, DOKR/PAK1, AKT/PI3K and AP-1 transcription factors, EGR1 and KLF2 [68]. GM-CSF plays an important role in wound healing, enhancing

VEGF expression, downregulate ANG1 and ANG2 expression, suppressing Tie2 phosphorylation and at early wound healing, leads to pericytes separation and high level of GM-CSF wound healing. Preserves VEGF expression while increasing the expression ratio of ANG1/ANG2, phosphorylation of Tie2, which results in higher pericyte coverage and greater integration of the underlying membrane, is required to inhibit blood vessel function [66]. Recent studies have shown that ginsenosides inhibit the expression of MMP saponin Rg1, ginsenoside Rh2, Rh, saponin Rh2 and Rd by negatively regulating MMP1, MMP2, MMP3, MMP7, MMP9, and MMP13 expression and cancer cell migration [3]. Inhibitors such as endostatin, angiostatin, interleukin-12, interleukin-1, interferons, interleukin-18 [4], prolactin [5], metalloprotease and retinoic acid inhibitors (Table 2) disrupt or help to remove the formed vascular vessels. While altering the balance toward angiogenesis inhibition, it can impair important physiological roles, such as embryo development and wound healing, and that intervention in wound healing is an important cancer concern that, based on the therapeutic goal of angiogenesis inhibition, may it is divided into two groups: Direct inhibitors that target growing endothelial cells and are in fact the main target of

16

integrin. Small molecular fragments e.g. endostatin, canastatin, tumstatin, arrestin, angiostatin are proteolytic products that degrade extracellular matrix and act as a direct inhibitor by inhibiting endothelial cell proliferation and migration induced by VEGF-A and PDGF. Whereas indirect inhibitors target tumor cells or tumor-associated stromal cells [4]. Recent studies have shown that ginseng has an inhibitory effect on tumor angiogenesis via direct inhibition of vascular endothelial cell proliferation, inhibition of tumor angiogenesis factors (mainly VEGF), pathway signal transduction, MMP activity inhibition, and expression enhancement of angiogenesis inhibitory factors [3].

Table 2. Illustration of angiogenesis inhibitory factors along with structural features, secretion source, signaling pathways and their function

Angiogenesis inhibitor	Structural feature	Source	Function	Signaling Route
Endostatin	Derived from XVII type collagen Polypeptide with 184 amino acids Kda20 [75].	It is made by proteolytic cleavage in type 18 collagen [73] .	It inhibits angiogenesis [70]. It suppresses cell cycle control and anti-apoptotic genes in endothelial cells [71]. It may grow on VEGF growth factors such as: BFGF and ADHD Inhibition of new cell growth by inhibition of cyclin D1 results in G1 cells stopping and undergoing apoptosis [71, 72]. It may inhibit specific metalloproteinase activation [73] . Reduces the FGF signal. The number of signaling pathways decreases Ras, Raf and P38, ERH1 activity [74].	JNK [69]

Interferons	Interferon alpha-165-166 and interferon alpha-166 have 146 amino acids and gamma interferon has 146 amino acids [79].	Immune leukocytes, lymphocytes, fibroblasts and other cell types [78].	They belong to the category of cytokines. They stimulate the immune system and increase the body's resistance to pathogens. They are involved in normal immune responses even in the absence of the virus, such as cancer. Interferons suppress angiogenesis and regulate endothelial cell proliferation by resetting angiogenesis stimuli [77].	JAK/STAT C3G/Rap1 PI3K [76]
IL-1	It is first synthesized as a precursor protein. Following proteolysis it is converted to a short-acting molecule, generally called IL-1 [83].	Macrophages, Monocytes, Dendritic Cells, Fibroblasts [82]	It is involved in inflammatory responses, rapid differentiation of white blood cells, inflammation, and production of phagocytic proteins [82].	TAK1, TRAF6, MEKK3, NF-KB, AP-1 JNK, P38, MAPK [80,81]
IL-12	It consists of 4 α-helices and is a HETERODIMERIC cytokine encoded by two separate IL-12A and IL-12B genes [86].	Macrophages [88], dendritic, neutrophils, human B-lymphoblastoid cells in response to antigen stimulation [86].	It has anti-angiogenic activity. It plays a role in stimulating TCELL function and stimulating the secretion of interferon-gamma, TNFα and natural killer cells. IL-4 depletion mediates IFN-1 suppression [85].	JAK/STAT [84]

18

Angiotensin	A 38 kDa fragment is larger than protein. It is one of the proteins of the beta-globulin group [90, 91].	It can be isolated from plasminogen by various metalloprotease, PSA, 13 kDa serine protease or 24 kDa endopeptidase [88].	It inhibits angiogenesis by directly affecting endothelial cells and proliferating and inducing apoptosis [88,89].	Its mechanism has not yet been accurately identified. But there are three suggested functional mechanisms [87].
Prolactin PRL	In humans there are three smaller cases of 4, 16, 22 kDa and several larger ones [96].	It is secreted from the pituitary lacto trophic cells [96].	It plays an important role in metabolism, immune system regulation and pancreatic development [92,93]. It helps to synthesize pulmonary surfactant in the fetal lungs at the end of pregnancy and to support fetal immunity by the mother's organs during pregnancy [94,95].	Through the prolactin receptor it acts by endocrine, autocrine and paracrine and cytokine receptors [92].
IL-18	It is first synthesized as a passive 24-kDa precursor. After intracellular processing by caspases, it becomes a mature 18 KDA biologically active molecule [95].	Hematopoietic cells and non-hematopoietic cells are capable of producing IL-18. [103] It is mainly produced by macrophages and a number of other cells [97].	It is a pro-inflammatory cytokine that reduces type 1 responses. It has an important role in activating macrophages and other cells. [97]. Impaired IL-18 regulation can induce autoimmune and inflammatory diseases [101,102].	NF-KB, STAT3 [97-100]

Signaling pathways inducing cancer angiogenesis

The purpose of this section is to provide an overview of angiogenesis-inducing mechanisms by which each factor can act in one or more of the following ways and explain the common pathways by which these factors can be activated that ultimately target They induce angiogenesis and cell survival.

The role of the MAPK / ERK signaling pathway in the induction of angiogenesis

The MAPK/ERK pathway is a chain of proteins in the cell that signal starts by attaching signaling molecules to the receptor at the cell surface and continues until the DNA is expressed in the nucleus and causes some changes [7]. This pathway, which is composed of numerous protein-forming proteins cascade is involved in the differentiation and proliferation of cells and apoptosis in eukaryotic cells [8]. Different cytokines can function in this way. G-CSF is one of these cytokines that is secreted by various tissues and stimulates survival, cell proliferation, differentiation and progressive function of neutrophils, resulting in neutrophil maturation [45]. G-CSF is expressed in placental tissues and trophoblastic cells. G-CSF functional receptors activate various signaling pathways including MAPK, PI3K, JAK/STAT in trophoblastic cell lines [45]. G-CSF activates the MAPK/ERK pathway by binding to its receptor and phosphorylating the cytosolic domain of G-CSFR. Activation of intermediate Grab proteins mediate the RAS pathway. RAS increases the proliferation and activation of kinases (RAF-MEK-ERK1/2), which eventually leads to cell proliferation [104].

MAPK is one of the pathways by which G-CSF can play a role in regulating the biological activities of trophoblast cells, including: migration, invasion and proliferation and cell differentiation [105]. FGF2 is another cytokine that can function through this pathway. This cytokine has been implicated in fetal growth, cell survival, widespread mutagenesis, tumor growth, and invasion [30,31]. FGF2 acts as signaling molecules that are activated by binding to FGF2 receptors, and these activated receptors bind to the cytosolic region of the receptor by employing specific molecules that bind to the phosphorylated tyrosine moiety. Stimulation of a number of signaling pathways leads to specific cellular responses, and then these FGF2 serve as docking sites for the uptake of a second free SH2 or PTB, protein adapter or signaling enzymes. By binding signaling complexes to activated receptors, phosphorylation cascades begin [33], which can eventually lead to tumor growth and invasion [31]. TNF-α is a cytokine that is involved in the acute phase response in the body and regulates immune cells, fever and tumor progression [48]. MAPK is one of the pathways by which TNF-α can function [47,106]. TNF by binding to its receptor, forms the RIP, TRAF2, TRADD complex.

TRAF2 activates JNK upstream kinases (TAK1, MEKK1, ASK1 and MLK2/MLK3 and activate the SRC, VAV, RAC, MLK2/3 axes, and these kinases eventually phosphorylate MKK7, which activate the JNK pathway. Activated JNK goes to the nucleus and activates transcription factors such as C-JUN and ATF2. Due to the changes that result from activation of these transcription factors, JNK can lead to cell proliferation and differentiation [47,106]. EGF is a cytokine that promotes growth, cell division and angiogenesis [27] and functions through activation of the ERK/MAPK pathway [26]. Mitogens and growth factors stimulate activation of tyrosine kinase receptors such as EGFR, which, after binding EGF to their receptor, activate subsequent Ras GTPase, which leads to phosphorylation of MAPK (RAS-RAF-MEK) and eventually leads to phosphorylation and activation of ERK. ERK phosphorylation results in activation of kinases and phosphorylation of a number of targets involved in the regulation of cell proliferation [107,108].

The role of the NF-KB signaling pathway in the induction of angiogenesis

NF-KB is found in almost all animal species and responds to stimuli such as: cytokines, stress, free radicals, bacterial or viral antigens, etc. NF-KB plays an important role in regulating the immune response to infections and, if left unregulated, causes inflammatory and autoimmune diseases, septic shock, and viral infections [11]. NF-KB is involved in modulating cellular processes. This pathway is stimulated by different signaling cascades and is involved in different cell cross-talk [12]. TNF-α is one of the cytokines that can act in this way. As explained in the previous section, TNF-α is a cytokine that is involved in the inhibition and development of tumors and immune responses [48]. TNF-α binds to its receptor at the cell surface by the uptake of TRADD, TRAF-2, and RIP, which complexes with TRAF-2, which in turn adsorbs the multifunctional protein IKK and the serine threonine kinase enables RIP to enable it. The inhibitory protein IKB normally binds to NF-KB and blocks its binding and is phosphorylated by IKK and degraded upon release of NF-KB. NF-KB is a heterodimeric transcription factor that transmits to the nucleus and stimulates transcription of a wide range of proteins involved in survival, cell proliferation, inflammatory response and anti-apoptotic factors [47]. IL-8 is another cytokine that is a potent enhancer of angiogenesis and phagocytosis and is known as neutrophil

chemotactic [59,60]. IL-8 induces reporter gene dependent NF-KB expression as well as expression of COX-2, VCAM-1, and ICAM-1. IL-8 induces IKB phosphorylation followed by degradation and translocation of P65. IL-8 can induce MAPK, JNK, C-JUN in a dose and time-dependent manner. The NF-KB activation induced by IL-8 is almost unaffected in cells transfected with TRADD, TRAF-2, or FADD, but inhibited by IKB, IKK, NIK, TRAF-6 predominantly transfected cells. Studies have shown that the activated NF-KB pathway induced by IL-8 is not dependent on TRAF-2 but is dependent on TRAF-6, which subsequently traps IRAK and activates IKK. IL-8-induced NF-KB activation is mainly mediated by interaction with TRAF-6 and partly by the Rho GTPase pathway. Activated genes may trigger one of the pathways of IL-8-induced inflammation and angiogenesis [109].

The role of the AKT signaling pathway in the induction of angiogenesis

AKT pathway kinases are involved in regulating a variety of cellular processes, including cell proliferation, cell survival and size, response to tissue invasion and angiogenesis. Many onco-proteins and tumor suppressors are involved in this pathway that are involved in cell signaling and metabolic regulation. AKT is a cell survival factor and partially inhibits cytochrome c release from mitochondria and has anti-apoptotic activity. It can also phosphorylate and deactivate the pro-apoptotic factor BAD and procaspase 9 [16]. TGF-α is a signaling molecule and one of the pathways that it can use to reach its goal is AKT signaling pathway [63]. TGF-α has been implicated in cell proliferation, wound healing, embryogenesis, angiogenesis, and tumorigenesis [64, 65] . TGF-α is a member of the EGF family, and TGF-α binds to its specific receptor, EGFR. EGFR itself is from the ErbB receptor family [110] . ERBB2, has no direct activating ligand and can be formed in the active state or activated by other members of the family such as EGFR after dimerization [111]. EGFR is dimerized and induces the intrinsic activity of the protein tyrosine kinase within the cell, eventually causing the auto phosphorylation of several tyrosine residues in the second C-terminal EGFR. This activation and signaling auto phosphorylation occurs due to the association of several proteins with phosphorylated tyrosine that are linked through the second SH2 phosphotyrosine. These signaling proteins can activate

several signaling pathways. One of these pathways is AKT, which eventually leads to DNA synthesis and can modulate processes such as proliferation, cell migration and adhesion [63,112] . G-CSF is a cytokine and hormone secreted by various tissues and can induce cell proliferation, differentiation and survival [45]. Phosphatidylinositol 3-kinase (PI3K) is activated by G-CSF. Recently, tyrosine kinase AKT has been identified as a target of PI3K. AKT has a second N-terminal regulation, called the second Pleckstrin Homology (PH), which is important for AKT activity. Phosphatidylinositol 3-4 bisphosphate, a product of PI3K, binds directly to the second AKT, PH, which eventually results in AKT activation. AKT has an important role in cell survival and enhances the active expression of AKT, inhibits apoptosis and is responsible for BAD phosphorylation. BAD inhibits the function of death through its association with the protein family 3-3-14, thereby playing a role in cell survival and proliferation [113].

Signaling pathways with inhibitory role of cancer angiogenesis

The purpose of this review is to elucidate the signaling pathway for angiogenesis

inhibition. These inhibitors can perform through one or more pathways. This section categorizes the factors that carry out the common path and provides a brief description of the features and signaling pathway.

The role of JAK-STAT signaling pathway in inhibition of angiogenesis

More than 50 cytokines work through the JAK-STAT orchestrate pathway, hematopoiesis, induction of inflammation and immune response control. Cytokines are secreted from glycoproteins that act as intercellular messengers, causing their target cells to proliferate, differentiate or grow. These cytokines are amplified and activated by binding to their specific receptors at the target cell surface and elucidating the intracellular signaling pathway of phosphotyrosine by kinases then by a second SH2-containing transcription factor [114]. Interleukin-12 is one of the cytokines involved in inhibiting angiogenesis, stimulating growth and function of T cell and stimulating the secretion of interferon-gamma, TNFα and natural killer cells [85]. JAK-STAT is the signaling pathway of IL-12, in which this cytokine binds to its receptor at the cell surface, which is a heterodimeric receptor,

which consist of IL-12RB2 and IL-12RB1. IL-12RB1 plays a key role in IL-12 function because it is present in activated T cells that are stimulated by cytokines that promote TH1 cells and are inhibited by cytokines that promote TH2 cells. Binding of IL-12p35 to the IL-12Rβ2 receptor and binding of IL-12 P40 to the IL-12β1 receptor cause changes in the structure that facilitate binding and activate JAK2 and TYK2, which are associated with both receptors. Phosphorylation and homodimerization at the IL-12 receptor lead to STAT4 signaling and activation, where STAT4 enters the nucleus and exerts its activity by affecting transcription factors [85,115]. Another inhibitor of angiogenesis is that interferons can act through this pathway. Interferons are a group of signaling proteins [116]. Interferons (IFN) suppress angiogenesis and endothelial cell proliferation by stimulating tumor cell-induced angiogenesis [77]. IFN activates the STAT signal transducer and interacts with its specific receptors. Some STATs are activated by type IFN1 and type IFN2, but each type of IFN can activate a specific STAT. The STAT pathway is the best signaling pathway for all interferons, following the classic JAK/STAT signaling pathway. JAK, together with the IFN receptor, phosphorylates STAT1, STAT2

and is then stimulated by interferon-stimulated gene factor 3 Interferon-Stimulated Gene Factor 3 (ISGF3) and interferon with STAT1, STAT2 and a third transcription factor called IRF-9, which is transferred into the cell nucleus; In the nucleus, it activates the ISRE transcription factor, which eventually exerts its effect [76].

The role of the JNK signaling pathway in the inhibition of angiogenesis

This pathway plays a key role in the cell proliferation and survival of cancer cell apoptosis. JNK increases with increasing NF-KB, JAK/STAT and other signaling molecules to promote cell survival. JNK positively regulates autophagy to counteract apoptosis and its effect on autophagy is related to expand the chemotherapy resistance. The progressive effect of JNK may be an immune-evasion mechanism mediated by transforming growth factor-β, toll-like receptors, interferon-gamma, autophagy, and JNK-dependent cell proliferation [18]. Endostatin is one of the angiogenesis inhibitors that uses this pathway [69]. Endostatin controls the cell cycle and suppresses anti-apoptotic genes in endothelial cells [71]. Endostatin inhibits

24

JNK-induced TNF activation in endothelial cells. TNF induces gene expression in many molecules involved in inflammation, angiogenesis, cell proliferation and induction of JNK activation. It is hypothesized that endostatin inhibits angiogenesis by blocking TNF signaling in endothelial cells [69]. Another cytokine that activates this pathway is IL-1, which is involved in the inflammatory response, differentiation and production of white blood cells [82] and can activate JNK transcription factor. Thus, mature IL-1α or IL-Iβ binds to IL-1R1 or IL-1RACP and

forms a heterodimeric receptor complex and then a second cytosolic region called toll (TIR) and Myeloid Differentiation primary response gene (88) (MYD88) forms a complex and finally results in activation of tumor necrosis factor receptor (TRAF6). The signal then goes to the nucleus and activates many transcription factors, such as NF-KB and JNK, and these factors exert their activity [80].
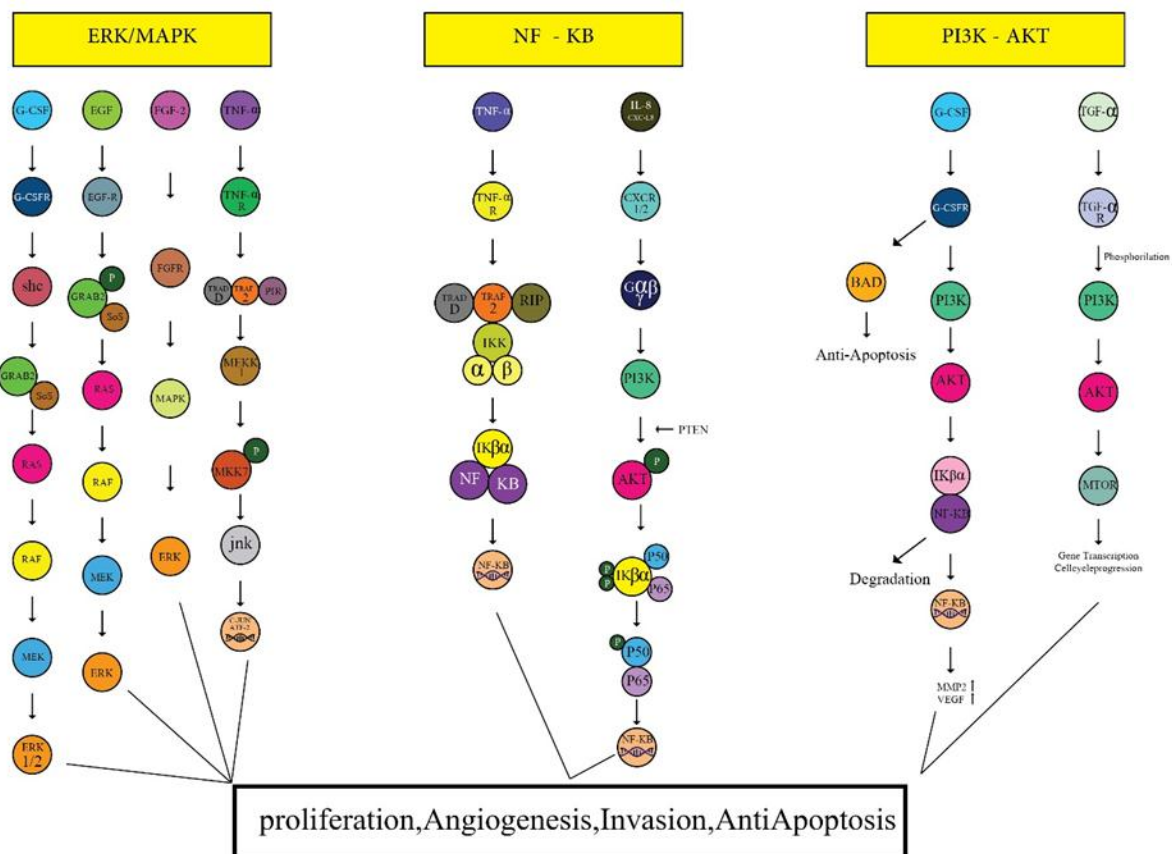
Figure 1.| The angiogenesis-inducing factors which induce cell angiogenesis, proliferation, and invasion, through different signaling pathways. G-CF, EGF, FGF2 and TNF-α can induce angiogenesis and cell proliferation through the ERK / MAPK signaling pathway. The signaling pathway for each inducible factor is plotted in the figure and the genes shared in the signaling pathway are with same color. NF-KB is another signaling pathway through which angiogenesis-inducing factors including TNF-α and IL-8 can induce cell proliferation, invasion and angiogenesis. PI3K-AKT is the next signaling pathway through which inducible factors such as G-CSF and TGF-α can mediate cell proliferation, invasion and angiogenesis. The purpose of this figure is to explain the signaling pathways that are effective in inducing angiogenesis that each of these factors can function through different signaling pathways. The common genes in the Figure 1 pathways are with same color and ultimately the factors and signaling pathways described above induce angiogenesis, proliferation, invasion and inhibition of apoptosis.
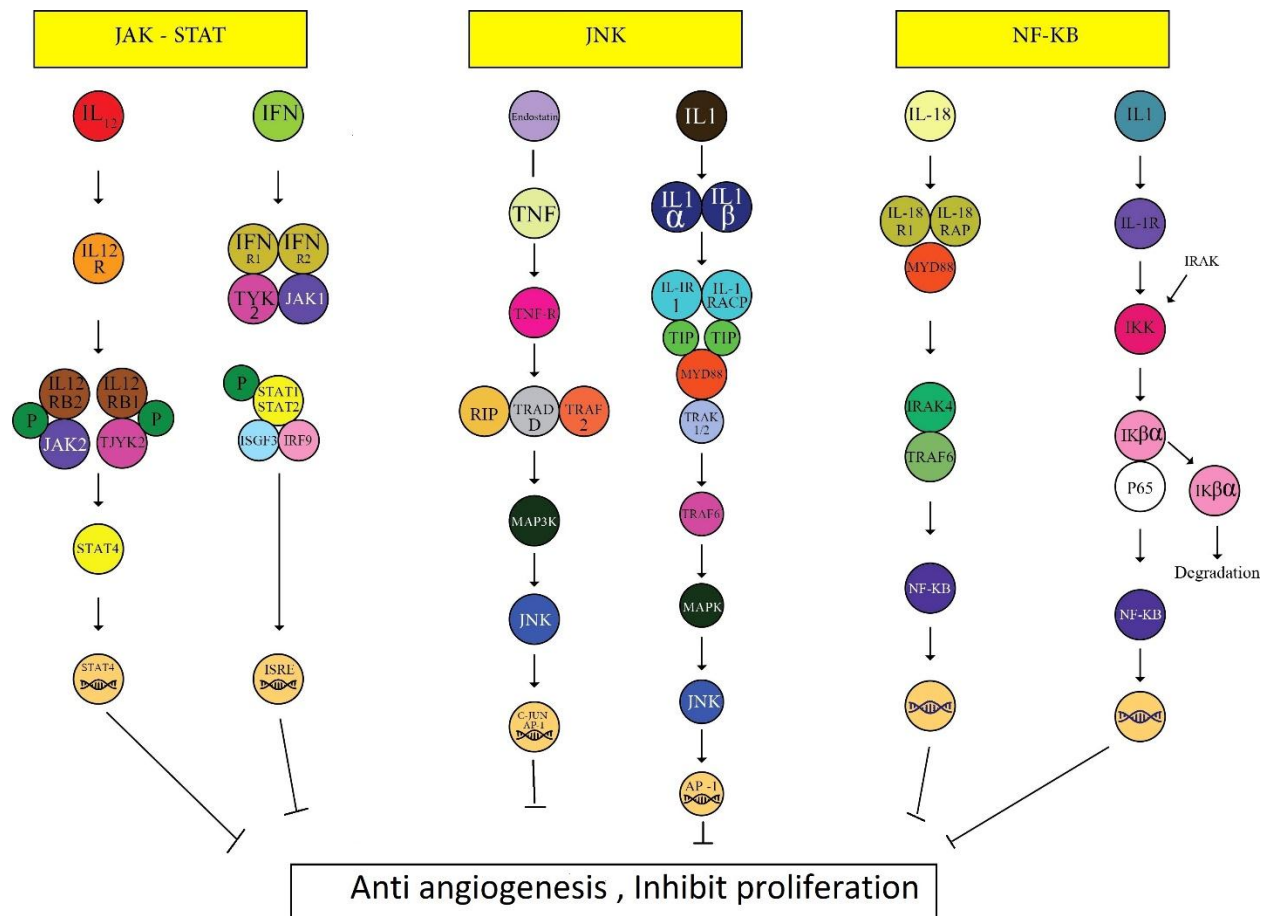

Figure 2. Various factors and signaling pathways which act as angiogenesis inhibitory agents. Figure 2 illustrates the signaling pathways through which various factors can inhibit angiogenesis, inhibit proliferation, and induce apoptosis. The JAK-STAT signaling pathway is one of the pathways by which IL-12 and IFN can inhibit angiogenesis and inhibit proliferation. JNK is another signaling pathway that factors such as endostatin and IL-1 can inhibit angiogenesis and inhibit proliferation. IL-18 and Il-1 are other angiogenesis inhibitors that NF-KB is one of the signaling pathways that these factors can inhibit cell proliferation and angiogenesis by that. The purpose of Fig. 2 is to illustrate the signaling pathways that eventually lead to the mentioned activities.

The role of the NF-KB signaling pathway in the inhibition of angiogenesis

NF-KB is a signaling pathway that can modulate cellular processes. The NF-KB pathway is stimulated by different signaling cascades and is involved in different interactions in the cell. The NF-KB signaling pathway controls inflammatory responses by TNF-α and IL-1 [12]. IL-1 and IL-18 are two cytokines that can activate the NF-KB pathway, IL-18 is a pro-inflammatory cytokine whose dysregulation can cause autoimmune and inflammatory diseases [101,102] .The IL-18 receptor is composed of an inducible component of IL-18RA that binds mature IL-18 with low affinity and binding to the IL-18RB receptor. IL-18 binds the IL-18RA ligand receptor and strengthens IL-18RB to form a high affinity complex through the second Toll Interleukin Receptor (TIR). This second signaling regulates the MYD88 adapter protein then activates and forms the complex of TRAF6 and IRAK4 and eventually activates proinflammatory and NF-KB pathways that affect intracellular transcription factors and these activating factors. Have been doing their task [98]. Another cytokine is the IL-1 pathway. This cytokine can be activated by different ways [80,81]. IL-1 is secreted by macrophages, monocytes and fibroblasts and is involved in inflammatory responses, differentiation and rapid production of white blood cells [80]. IL-1 binds to its receptor, which interacts with interleukin-1 receptor kinase (IRAK and TLR) to activate IKK. IRAK-1 enhances NF-KB transcriptional activity by binding to the IKβ and NF-KB regulated gene promoter and also enhances binding of the NF-KB P65 subunit to responsive elements in the IKβa promoter and ultimately, after IKβα degradation, transduces NF -KB is inserted into the nucleus where NF-KB activates, activating transcription factors and exerting its effect on DNA [117].

CONCLUSION

Cytokines involved in angiogenesis that can inhibit and induce angiogenesis have been implicated in the inhibition or induction of angiogenesis through various signaling pathways. The purpose of this article is to describe common signaling pathways between cytokines involved in angiogenesis. Many drugs can affect these signaling pathways by affecting one or more of the components of signaling pathways that alter the activity of the genes involved in these signaling pathways. MAPK/ERK is one of the signaling pathways through which cytokines such as

G-CSF, FGF2, and TNF-α work their way and induce cell proliferation, inhibition of apoptosis and angiogenesis. DHA is a derivative of artemisinin and has anti-angiogenic activity and induces apoptosis through P38 MAPK activation and transcriptional repression and affects transcription factors including C-MYC and C-FOS. Other factors including TNF-α, 1L-8, IL-18 and IL-1 can function through the NF-KB signaling pathway that inhibits angiogenesis, inhibits proliferation, IL-18 and IL-1 cytokines. And TNF-α and IL-8 cytokines are involved in inducing cell proliferation and inducing angiogenesis. metformin and ginsenoside Rk1 are among the drugs that affect this signaling pathway. Metformin inhibits NF-KB signaling by inhibiting LCA-stimulated ROS production. Rk1 can inhibit the NF-KB signaling pathway by affecting the cell cycle and stopping it at G1 stage and increasing BAX and PARK expression and decreasing BCL2 expression. AKT is one of the signaling pathways through which factors such as TGF-α and G-CSF can induce angiogenesis. Aloperine is an example of a drug that affects this signaling pathway that inhibits cell proliferation and cell cycle arrest at the G2/M stage and ultimately inhibits this pathway. Factors such as endostatin and IL-1 can inhibit

angiogenesis and induce apoptosis through the JNK signaling pathway. Erianin has an antitumor and anti-angiogenic effect, which works by inhibiting cell proliferation and inducing apoptosis by ROS on treated cells. IFN and IL-12, which are involved in the inhibition of angiogenesis and can function through the JAK-STAT signaling pathway. JQ1 is a drug that can affect this pathway and by affecting C-MYC induce apoptosis and inhibits the proliferation. If each of these factors be out of balance, can cause a wide range of cancers. So the inhibition of angiogenesis can be an effective therapeutic strategy in the treatment of cancer.

REFERENCES

[1]. Li X, et al. Cinobufagin suppresses colorectal cancer angiogenesis by disrupting the endothelial mammalian target of rapamycin/hypoxia-inducible factor 1α axis. *Cancer Sci*, 2019. 110(5): 1724.

[2]. Morbidelli L, .Terzuoli E, Donnini S. Use of nutraceuticals in angiogenesis-dependent disorders. *Molecules,* 2018. 23(10): 2676.

[3]. Zou, J, et al. Ginseng and Angiogenesis: Promotion or

Inhibition? *Food,* 2019. 1(1): 22-29.

[4]. Melegh, Z. and S. Oltean, *Targeting Angiogenesis in Prostate Cancer.* IJMS, 2019. 20(11): 2676.

[5]. Daniel S. How can angiogenesis inhibitors be used to treat cancer?

[6]. Nisar S, et al. Exploring Dysregulated Signaling Pathways in Cancer. *Curr Pharm Des,* 2020.

[7]. Orton RJ, et al. Computational modelling of the receptor-tyrosine-kinase-activated MAPK pathway. *Biochem J,* 2005. 392(2): 249-261.

[8]. Liang YJ, Yang WX. Kinesins in MAPK cascade: how kinesin motors are involved in the MAPK pathway? *Gene*, 2018.

[9]. Dong, F, et al. Dihydroartemisinin inhibits endothelial cell proliferation through the suppression of the ERK signaling pathway. *Int J Mol Med,* 2015. 35(5): 1381-87.

[10]. Zhang Y, Cao H. Monomeric C-reactive protein affects cell injury and apoptosis through activation of p38 MAPK in human coronary artery endothelial cells. *Bosnian J Basic Med,* 2020.

[12]. Biswas R, Bagchi A. NFkB pathway and inhibition: an overview. *CMB*, 2016. 6(1): 1-20.

[13]. Nguyen TT, et al. Metformin inhibits lithocholic acid-induced interleukin 8 upregulation in colorectal cancer cells by suppressing ROS production and NF-kB activity. *Sci Reports,* 2019. 9(1): 1-13.

[14]. He J, et al. Development of PD-1/PD-L1 pathway in tumor immune microenvironment and treatment for non-small cell lung cancer. *Sci Reports,* 2015. 5(1): 1-9.

[15]. Hu M, et al. Ginsenoside Rk1 induces apoptosis and downregulates the expression of PD-L1 by targeting the NF-κB pathway in lung adenocarcinoma. *Food Funct,* 2020.

[16]. Altomare DA, Testa JR. Perturbations of the AKT signaling pathway in human cancer. *Oncogene,* 2005. 24(50): 7455.

[17]. Liu JS, et al. Aloperine induces apoptosis and G2/M cell cycle arrest in hepatocellular carcinoma cells through the PI3K/Akt signaling pathway. *Phytomedicine,* 2019. 61: 152843.

[18]. Weston CR, Davis RJ. The JNK signal transduction pathway. *Curr.*

Opin. Cell Biol, 2007. 19(2): 142-49.

[19]. Mitra AD, et al. 1α, 25-Dihydroxyvitamin-D3-3-bromoacetate regulates AKT/mTOR signaling cascades: a therapeutic agent for psoriasis. *JID,* 2013. 133(6): 1556-64.

[20]. Seki, E., D.A. Brenner, and M. Karin, A liver full of JNK: signaling in regulation of cell function and disease pathogenesis, and clinical approaches. *Gastroenterol*, 2012. 143(2): 307-20.

[21]. Mo, C., D. Shetti, and K. Wei, Erianin inhibits proliferation and induces apoptosis of HaCaT cells via ROS-mediated JNK/c-Jun and AKT/mTOR signaling pathways. *Molecules,* 2019. 24(15): 2727.

[22]. Xin, et al., The role of JAK/STAT signaling pathway and its inhibitors in diseases. *Int. Immunopharmacol,* 2020. 80: 106210.

[23]. Vita, M. and M. Henriksson. The Myc oncoprotein as a therapeutic target for human cancer. *Semin Cancer Biol.* 2006.

[24]. Bagratuni, T, et al. JQ1 inhibits tumour growth in combination with cisplatin and suppresses JAK/STAT signalling pathway in

ovarian cancer. *Eur J Cancer,* 2020. 126: 125-35.

[25]. Filippakopoulos, et al. Selective inhibition of BET bromodomains. *Nature,* 2010. 468(7327): 1067-73.

[26]. Fallon, JH, et al. Epidermal growth factor immunoreactive material in the central nervous system: location and development. *Science,* 1984. 224(4653): 1107-9.

[27]. Cohen, S. The epidermal growth factor (EGF). *Cancer*, 1983. 51(10): 1787-91.

[28]. Harris, R.C., E. Chung, and R.J. Coffey, EGF receptor ligands, in The EGF Receptor Family. 2003, Elsevier. 3-14.

[29]. Ornitz, D.M. and N. Itoh, The fibroblast growth factor signaling pathway. *Wiley Interdiscip Rev Dev Biol,* 2015. 4(3): 215-66.

[30]. Kühn, M.C, et al. Adipocyte-secreted factors increase osteoblast proliferation and the OPG/RANKL ratio to influence osteoclast formation. *Mol Cell Endocrino,* 2012. 349(2): 180-88.

[31]. House, SL, et al. Cardiac-specific overexpression of fibroblast growth factor-2 protects against myocardial dysfunction and infarction in a murine model of low-flow

ischemia. *Circulation,* 2003. 108(25): 3140-48.

[32]. Perez, J.A., et al. A new role for FGF2 as an endogenous inhibitor of anxiety. *J Neurosci,* 2009. 29(19): 6379-87.

[33]. Yun, YR, et al. Fibroblast growth factors: biology, function, and application for tissue regeneration. *J Tissue Eng,* 2010. 1(1): 218142.

[34]. Florkiewicz, R, et al. Basic fibroblast growth factor gene expression. *Ann N Y Acad Sci,* 1991. 638(1): 109-26.

[35]. Derynck, R., Y. Zhang, and X.-H. Feng, Transcriptional activators of TGF-β responses: *Smads. Cell*, 1998. 95(6): 737-40.

[36]. Massagué, J., TGFβ signalling in context. *Nat Rev Mol Cell Biol,* 2012. 13(10): 616.

[37]. Nakao, A., et al., Identification of Smad7, a TGFβ-inducible antagonist of TGF-β signalling. *Nature*, 1997. 389(6651): 631.

[38]. Massagué, J., S.W. Blain, RS Lo. TGFβ signaling in growth control, cancer, and heritable disorders. *Cell ,*2000; 103: 295-309.

[39]. Shibuya, M. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) signaling in angiogenesis: a crucial target for

anti-and pro-angiogenic therapies. *Genes Cancer*, 2011. 2(12): 1097-1105.

[40]. Ferrara, N., et al. Molecular and biological properties of the vascular endothelial growth factor family of proteins. *Endocr Rev,* 1992. 13(1): 18-32.

[41]. Neufeld, G., et al. Vascular endothelial growth factor (VEGF) and its receptors. *FASEB J,* 19; 99: 13: 9-22.

[42]. Verheul, H., et al. Platelet: transporter of vascular endothelial growth factor. *Clin Cancer Res,* 1997. 3(12): 2187-90.

[43]. Sunderkötter, C., et al. Macrophages and angiogenesis. *J leukocyte Biol,* 1994; 55: 410-22.

[44]. Frank, S, et al. Regulation of vascular endothelial growth factor expression in cultured keratinocytes. Implications for normal and impaired wound healing. *J Biol Chem,* 1995. 270(21): 12607-13.

[45]. Thomas, J., F. Liu, and D.C. Link. Mechanisms of mobilization of hematopoietic progenitors with granulocyte colony-stimulating factor. *Curr Opin Hematol*, 2002. 9(3): 183-89.

31

[46]. Chen, G. and D.V. Goeddel. TNF-R1 signaling: a beautiful pathway. *Science,* 2002; 296(5573):1634-35.

[47]. Kant, S., et al. TNF-stimulated MAP kinase activation mediated by a Rho family GTPase signaling pathway. *Genes Dev,* 2011. 25(19): 2069-78.

[48]. Swardfager, W., et al. A meta-analysis of cytokines in Alzheimer's disease*. Biol Psychiatry*, 2010. 68(10): 930-41.

[49]. Gahring LC, et al. Neuronal expression of tumor necrosis factor alpha in the OVOUJI fme brain. *Neuroimmunomodulation,* 1996. 3(5): 289-303.

[50]. Kriegler, M., et al. A novel form of TNF/cachectin is a cell surface cytotoxic transmembrane protein: ramifications for the complex physiology of TNF. *Cell,* 1988. 53(1): 45-53.

[51]. Tang MC. Hung, J Klostergaard. Human pro-tumor necrosis factor is a homotrimer. *Biochem,* 1996. 35(25): 8216-25.

[52]. Khurana R, et al. Placental growth factor promotes atherosclerotic intimal thickening and macrophage accumulation. *Circulation,* 2005. 111(21): 2828-36.

[53]. Khalil, A., et al. Effect of antihypertensive therapy with alpha methyldopa on levels of angiogenic factors in pregnancies with hypertensive disorders. *Plos one*, 2008. 3(7): 2766.

[54]. Nakamura, T. Structure and function of hepatocyte growth factor. *Prog Growth Factor Res,* 1991. 3(1): 67-85.

[55]. Bottaro, D. ,et al., *Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product.* Science, 1991. 251(4995): 802-804.

[56]. Gallagher J, M. Lyon. Molecular structure of heparan sulfate and interactions with growth factors and morphogens. Proteoglycans: structure, biology and molecular interactions, 2000: 27-59.

[57]. Rottner M, J.-M. Freyssinet, and M.C. Martínez, Mechanisms of the noxious inflammatory cycle in cystic fibrosis. *Respir Res,* 2009. 10(1): 23.

[58]. Ang Z, et al. Novel AU-rich proximal UTR sequences (APS) enhance CXCL8 synthesis upon the induction of rpS6 phosphorylation. *Plos Genetics,* 2019. 15(4): 1008077.

[59]. Brat, D.J., A.C. Bellail, and E.G. Van Meir. The role of interleukin-8 and its receptors in gliomagenesis and tumoral angiogenesis. *J Neuro Oncol,* 2005. 7(2): 122-33.

60]. Modi WS, et al. Monocyte-derived neutrophil chemotactic factor (MDNCF/IL-8) resides in a gene cluster along with several other members of the platelet factor 4 gene superfamily. *J Hum Genet,* 1990. 84(2): 185-87.

[61]. Dixit, N. and S.I. Simon. Chemokines, selectins and intracellular calcium flux: temporal and spatial cues for leukocyte arrest. *Front. Immunol,* 2012. 3: 188.

[62]. Hedges J, C.A .Singer, and W.T. Gerthoffer. Mitogen-activated protein kinases regulate cytokine gene expression in human airway myocytes. *Am J Respir Cell Mol* Biol, 2000. 23(1): 86-94.

[63]. Oda K, et al. A comprehensive pathway map of epidermal growth factor receptor signaling. *Mol Sys Biol*, 2005. 1(1).

[64]. Ferrer I, et al. Transforming growth factor-α (TGF-α) and epidermal growth factor-receptor (EGF-R) immunoreactivity in normal and pathologic brain. *Prog Neurobiol,* 1996. 49(2): 99-123.

[65]. McInnes C, et al. Structure-based minimization of transforming growth factor-α (TGF-α) through NMR analysis of the receptor-bound ligand Design, Solution Structure, and activity of TGF-α 8–50. *J Biol Chem,* 1998. 273(42): 27357-63.

[66]. Fallah A, et al. Therapeutic targeting of angiogenesis molecular pathways in angiogenesis-dependent diseases. *Biomed Pharmacother,* 2019. 110: 775-785.

[67]. Tahergorabi Z. and M. Khazaei. A review on angiogenesis and its assays. *Iran J Basic Med Sci,* 2012. 15(6): 1110.

[68]. Sanchez, V., et al., Negative regulation of angiogenesis by novel micro RNAs. *Pharmacol Res,* 2019. 139: 173-81.

[69]. Yin G, et al. Endostatin gene transfer inhibits joint angiogenesis and pannus formation in inflammatory arthritis. *Mol Ther,* 2002. 5(5): 547-54.

[70]. O'Reilly MS, et al. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. *Cell,* 1997; 88: 277-85.

[71]. Hanai Ji, et al. Endostatin causes G1 arrest of endothelial cells through inhibition of cyclin D1. *J Biol Chem,* 2002. 277(19): 16464-69.

[72]. Dhanabal M, et al. Cloning, Expression, andin VitroActivity of Human Endostatin. *Biochem Biophys Res Commun,* 1999. 258(2): 345-52.

[73]. Felbor, U., et al. Secreted cathepsin L generates endostatin from collagen XVIII. *EMBO J*, 2000. 19(6): 1187-94.

[74]. Sudhakar A, et al. Human tumstatin and human endostatin exhibit distinct antiangiogenic activities mediated by αvβ and α5β1 integrins. *PNAS,* 2003. 100(8): 4766-71.

[75]. Folkman J. Antiangiogenesis in cancer therapy—endostatin and its mechanisms of action. *Exp Cell Res,* 2006. 312(5): 594-607.

[76]. Platanias LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. *Nat Rev Immunol,* 2005. 5(5): 375.

[77]. Parkin J. and B. Cohen. An overview of the immune system. *The Lancet,* 2001. 357(9270): 1777-89.

[78]. Levy D.E., I.J. Marié, and J.E. Durbin. Induction and function of type I and III interferon in response to viral infection. *Curr Opin Virol,* 2011. 1(6): 476-86.

[79]. Liu YJ. IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. *Annu Rev Immunol,* 2005. 23: 275-306.

[80]. Weber A, Wasiliew, and M. Kracht. Interleukin-1 (IL-1) pathway. *Sci. Signal*, 2010. 3(105).

[81]. Simi A, et al. Interleukin-1 and inflammatory neurodegeneration. 2007, *Port. Press Lim.*

[82]. Contassot, E., H.-D. Beer, and L.E. French, Interleukin-1, inflammasomes, autoinflammation and the skin. *Swiss Med Wkly,* 2012; 142(2122).

[83]. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood,* 2011. 117(14): 3720-32.

[84]. Kaliński, et al. IL-12-deficient dendritic cells, generated in the presence of prostaglandin E2, promote type 2 cytokine production in maturing human naive T helper cells. *J Immunol,* 1997. 159(1): 28-35.

[85]. Wang KS, D.A. Frank, and J. Ritz, Interleukin-2 enhances the response

of natural killer cells to interleukin-12 through up-regulation of the interleukin-12 receptor and STAT4. *Blood*, 2000. 95(10): 3183-90.

[86]. Hsieh CS, et al. Development of TH1 CD4+ T cells through IL-12 produced by Listeria-induced macrophages. *Science,* 1993. 260(5107):547-49.

[87]. Moser TL, et al. Endothelial cell surface F1-FO ATP synthase is active in ATP synthesis and is inhibited by angiostatin. *PNAS,* 2001. 98(12): 6656-61.

[88]. Redlitz A, G. Daum, and E.H. Sage. Angiostatin diminishes activation of the mitogen-activated protein kinases ERK-1 and ERK-2 in human dermal microvascular endothelial cells. *J Vas Res,* 1999. 36(1): 28-34.

[89]. Grandi F, et al. Hierarchical mechanochemical switches in angiostatin. *Chembiochem,* 2006. 7(11): 1774-82.

[90]. O'Reilly MS, et al. Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. *Cell,* 1994. 79(2): 315-28.

[91]. Cao, Y., et al. Kringle domains of human angiostatin characterization of the anti-proliferative activity on endothelial cells. *J Biol Chem,* 1996. 271(46): 29461-67.

[92]. Bole-Feysot C, et al. Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. *Endocr,* 1998. 19(3): 225-68.

[93]. BATES RW, O. Riddle, The preparation of prolactin. *J Pharmacol Exp Ther*, 1935. 55(3): 365-71.

[94]. Shingo T, et al. Pregnancy-stimulated neurogenesis in the adult female forebrain mediated by prolactin. *Science,* 2003. 299(5603): 117-20.

[95]. Gu Y, et al. Activation of interferon-γ inducing factor mediated by interleukin-1β converting enzyme. *Science,* 1997. 275(5297): 206-209.

[96]. Lucas B, et al. Null mutation of the prolactin receptor gene produces a defect in maternal behavior. *Endocrinol*, 1998. 139(10): 4102-7.

[97]. Dinarello CA. Interleukin-18. *Methods,* 1999. 19(1) : 121-32.

[98]. Kaplanski G. Interleukin-18: Biological properties and role in

disease pathogenesis. *Immunol Rev,* 2018. 281(1): 138-53.

[99]. Garlanda C, HJ. Anders, and A. Mantovani. TIR8/SIGIRR: an IL-1R/TLR family member with regulatory functions in inflammation and T cell polarization. *Trends Immunol,* 2009. 30(9): 439-46.

[100]. Jia, H., J. Liu, and B. Han. Reviews of interleukin-37: functions, receptors, and roles in diseases. *Biomed Res,* 2018.

[101]. Baker KJ, A. Houston, and E. Brint. IL-1 family members in cancer; two sides to every story. *Front Immunol*, 2019. 10: 1197.

[102]. Fabbi, M., G. Carbotti, and S. Ferrini. Context-dependent role of IL-18 in cancer biology and counter-regulation by IL-18B. *J leukocyte Biol*, 2015. 97(4): 665-675.

[103]. Nakamura K, et al. Endotoxin-induced serum factor that stimulates gamma interferon production. *Infect Immun,* 1989. 57(2): 590-95.

[104]. Dwivedi K.D. Greis. Granulocyte colony-stimulating factor receptor signaling in severe congenital neutropenia, chronic neutrophilic leukemia, and related malignancies. *Exp Hematol,* 2017. 46: 9-20.

[105]. Furmento VA, et al. Granulocyte colony-stimulating factor (G-CSF) upregulates β1 integrin and increases migration of human trophoblast Swan 71 cells via PI3K and MAPK activation. *Exp Cell Res,* 2016. 342(2): 125-34.

[106]. Gaur U, Aggarwal BB. Regulation of proliferation, survival and apoptosis by members of the TNF superfamily. *Biochem*, 2003. 66(8): 1403-8.

[107]. Meloche S, Pouysségur J. The ERK1/2 mitogen-activated protein kinase pathway as a master regulator of the G1-to S-phase transition. *Oncogene, 7(22)*: 3227.

[108]. Chambard JC, et al. ERK implication in cell cycle regulation. *BBA-Mol Cell Res,* 2007. 1773(8): 1299-1310.

[109]. Manna SK, Ramesh GT. Interleukin-8 induces nuclear transcription factor-κB through a TRAF6-dependent pathway. *J Biol Chem,* 2005. 280(8): 7010-21.

[110]. Zhang H, et al. ErbB receptors: from oncogenes to targeted cancer therapies. *J Clin Investig,* 2007. 117(8): 2058.

[111]. Kennedy SP, Han JZ, Portman N, Nobis M, Hastings JF. Targeting promiscuous heterodimerization overcomes innate resistance to ERBB2 dimerization inhibitors in breast cancer. *Breast Cancer Res*, 2019; *21*(1), 43.

[112]. Downward J, Parker, Waterfield M. Autophosphorylation sites on the epidermal growth factor receptor. *Nature*, 1984; 311(5985): 483.

[113]. Dong F, Larner AC. Activation of Akt kinase by granulocyte colony-stimulating factor (G-CSF): evidence for the role of a tyrosine kinase activity distinct from the Janus kinases. *Blood*, 2000. 95(5): 1656-62.

[114]. Morris R, Kershaw NJ, Babon JJ. The molecular details of cytokine signaling via the JAK/STAT pathway. *PROTEIN SCI,* 2018. 27(12): 1984-2009.

[115]. Moschen AR, Tilg H. Raine, IL-12, IL-23 and IL-17 in IBD: immunobiology and therapeutic targeting. *Nat Rev Gastroenterol Hepatol,* 2019. 16(3): 185-96.

[116]. De Andrea M et al. The interferon system: an overview. *Eur. J. Paediatr. Neurol,* 2002; 6: 41-46.

[117]. Noor HB, Mou NA, Salem L, Shimul MF, Biswas S, Akther R, Khan S, Raihan S, Mohib M. 2020. Anti-inflammatory Property of AMP-activated Protein Kinase. *Antiinflamm Antiallergy Agents Med Chem*, 2020; *19*(1):2-41.