

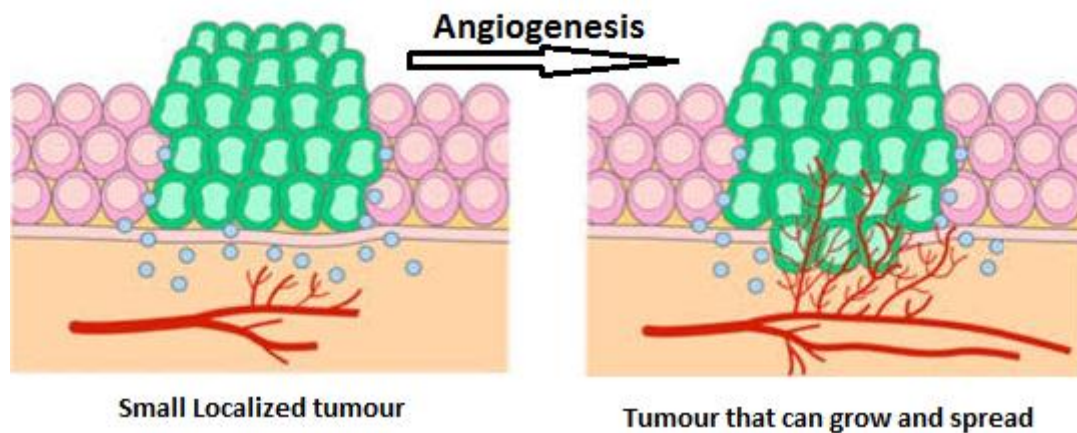
### **Study on Molecular basis of Cancer induced angiogenesis**

**ABSTRACT:** Cancer is a disease of faulty cells, that have excessive potential of excessive proliferation without apparent relation to the physiological organ. Cancer is a multi-factorial multi-staged and multi-mechanistic complex process. It entails the interaction of the environmental and host factors within the inception, progression of manifestation. Inherited genetic inclinations contribute extensively to 5-10 percent of breast cancers and 5- 13 percent of colon cancers incidences. In the industrialized nations, kind of 7 percent of most cancers deaths are resulting from viral infections; four percent to occupational hazards; 2 percent to sunlight; 2 percentage to pollutions of air, water, and soil; and less than 1 percentage to food components and business products. This review provides an overview that summarizes the current state of research on micro metastatic state with solid tumors.

**Keywords:** Etiology, Epidemiology, Cancer, Angiogenesis, MMP, Hypoxia.

**INTRODUCTION:** Many chemical and bodily cancer agents can set off one or extra of a variety of mutations in cells when given chronically [1]. A desirable variety of most cancers causing chemical substances are man-made and used either as business dealers, insecticides, pharmaceutical chemical substances or as meals components [2]. Carcinogens are extremely diverse systems and include each natural and synthetic product [3]. All chemical carcinogens are surprisingly reacting electrophiles that react with the electron wealthy atoms like RNA, DNA and protein [4]. Metals inclusive of arsenic and arsenic compounds, chromium, nickel, cadmium and beryllium can result in the improvement of lung and prostate cancers [5]. Physical carcinogens along with X-ray and UV ray may additionally purpose the formation of pyrimidine dimmers, apurinic web sites with consequent smash in DNA and formation of loose radicals, which motive destroy, leading to somatic mutations [6]. A big number of DNA and RNA viruses have proved to be oncogenic in animals, while only some viruses were connected with human cancer [7]. The most lifestyles-threatening aspects of the oncogenic procedure is metastasis [8]. Even although the clinical significance of such expression of the malignant phenotype has been well appreciated, advances in know-how the molecular mechanisms

involved in metastasis have lagged in the back of different trends within the cancer subject [Figure 1] [9].



**Figure 1:** Tumors induce blood vessel growth in promoting angiogenesis, Image courtesy of the National Cancer Institute, Cancer Information and Support Network.

**MATRIX METALLOPROTEINASES:** Matrix metalloproteinases (MMPs), are a family of related zinc metallo endopeptidases that function in the turnover of components of the extracellular matrix [10]. These enzymes play a central role in the normal embryogenesis and tissue remodeling and in many diseases such as arthritis, cancer, periodontitis, glomerulonephritis, encephalomyelitis, atherosclerosis and tissue ulceration [11]. Tissue inhibitors of metalloproteinases (TIMPs) are the principle physiologic inhibitors of the MMPs [12]. TIMPs are secreted proteins that complex with character MMPs and regulate the pastime of person MMPs [13]. Together, the MMPs and TIMPs shape a complex organic gadget strictly controlling degradation of extracellular matrix [14]. The MMPs and TIMPs have an extensive position in facilitating tumor invasion and metastasis, no longer most effective through their direct function in degrading extracellular matrix but also by way of interaction with other biological structures implicated in tumor invasion, such as cell adhesion molecules, cytoskeletal proteins and boom elements [15].

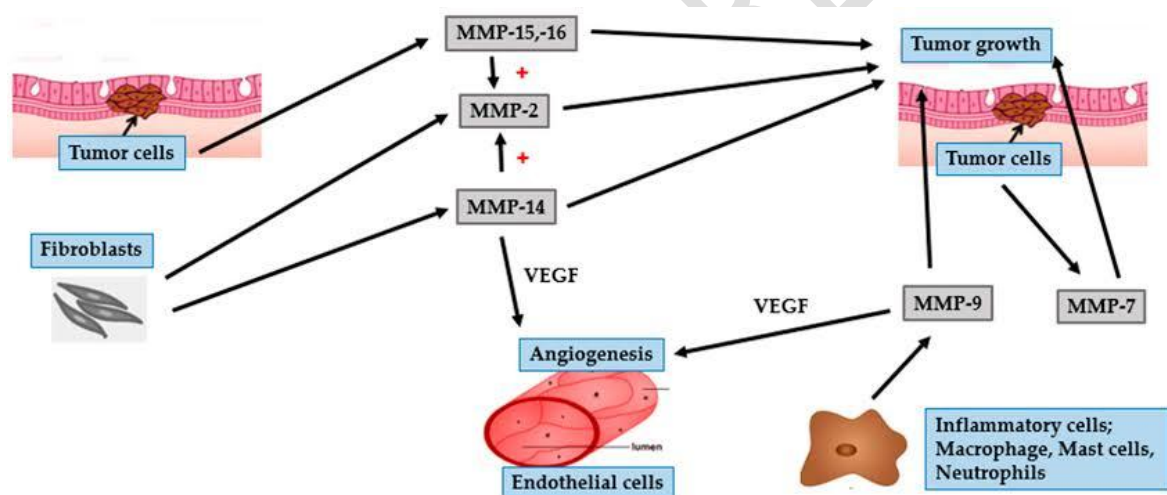
**TIMP-1 AND 2:** TIMP-1 mRNA expression is up-regulated in many human cancer sorts and in a few instances correlates with greater severe clinical outcome e.g., colorectal carcinoma, non-small cell lung carcinoma and breast carcinoma [16]. Studies in experimental mouse fashions have revealed sarcastically that TIMP-1 can show off proneoplastic and antineoplastic effects at some stage in number one and metastatic tumor improvement [17]. TIMP-2 is a multifunctional inhibitor of angiogenesis, tumor boom and tumor invasion [18]. These

techniques involve not handiest tumor cells themselves however additionally the modulation of complex tumor-host interactions [19]. Because the host reaction to the tumor microenvironment can act both to facilitate or to inhibit tumor invasion and spread, manipulating those host reaction elements has grown to be a prime focus of novel anticancer strategies [20]. Although TIMP-2 can block the action of MMPs, it is able to also depend on MMP-unbiased mechanisms that modulate tumor-host interactions [21]. TIMP-2 has an immediate position in regulating tyrosine kinase-type growth issue receptor activation [22].

**ANGIOGENESIS:** Angiogenesis, the formation of new capillaries, is many of the key occasions in numerous detrimental pathologic procedures, inclusive of tumor growth, metastasis, arthritis and so on as well as in physiologic tactics, like organ growth and development, wound recovery and reproduction [23]. Blood vessels are the first organ in the embryo and the largest network in our body, but they are also frequently lethal [24]. When dysregulated, the formation of recent blood vessels contributes to severe malignant, ischemic, inflammatory, infectious and immune disorders [25]. Molecular insights into these procedures are being generated at unexpectedly increasing pace, imparting new therapeutic opportunities which are currently being evaluated [26].

**TUMOR GROWTH AND METASTASIS:** Angiogenesis is needed for invasive tumor growth and metastasis and constitutes a vital point within the manipulate of cancer development [27]. For tumors to broaden in length and reach metastatic ability they have to make an angiogenic switch via perturbing the nearby stability of proangiogenic and antiangiogenic factors [28]. Tumors that have become neovascularized frequently express increased ranges of proangiogenic proteins, along with vascular endothelial increase factor (VEGF) and simple fibroblast boom factor (bFGF) [29]. The expression of proangiogenic proteins may be brought on by numerous elements, including hypoxia, activation of oncogenes or inactivation of tumor suppressor genes [30]. In some tumors, the angiogenic transfer is the end result of down law of antiangiogenic elements [31]. In most grownup tissues, the stability between proangiogenic and anti-angiogenic signaling favors vasculature [32]. In a few instances, however, proangiogenic activities prevail, ensuing inside the tumor vascularization and metastatic growth [33]. Two general techniques have been used inside the development of antiangiogenic traders: inhibition of proangiogenic issue and therapy with endogenous inhibitors of angiogenesis [34].

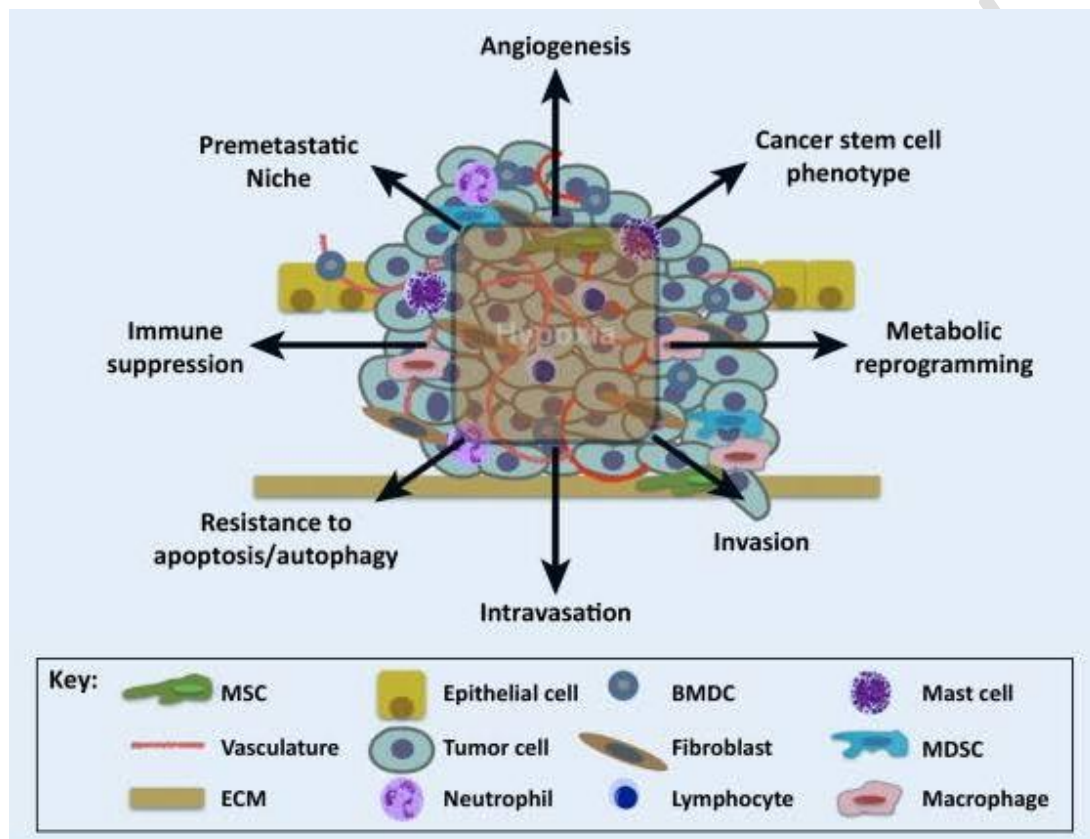
**VASCULAR ENDOTHELIAL GROWTH ELEMENT:** Solid tumors are multi compartmentalized systems, consisting of three major compartments: cancer and stromal cells, the extracellular matrix (ECM), and the vasculature [35]. The volumes of each of these components vary relying at the foundation and length of the tumor and the organ in which primary tumor develops [36]. Tumors require vasculature to benefit get entry to oxygen and other nutrients, permitting boom and metastasis [37]. VEGF (vascular endothelial growth factor) has been shown to be one of the most potent angiogenic factors produced through tumor cells [38]. It binds to endothelial cell surface receptors and turns on numerous functions of the mobile, which includes angiogenesis [39]. VEGF, also referred to as vascular permeability element (VPF or VEGFA) is the critical and significant regulator of angiogenesis [40]. The other participants of the VEGF own family, VEGF-B, VEGF-C, VEGF-D and PIGF also play a position in angiogenesis [41]. It can up-modify expression of adhesion molecules on vascular endothelium Figure 2 [42].



**Figure 2:** Role of MMPs in tumor growth and progression to angiogenesis [43].

**ROLE OF HYPOXIA:** Beyond a certain length, easy diffusion of oxygen to metabolizing tissues turns into inadequate [44]. The increased rate of cell division in cancer necessitates metabolic pathways to meet the demands of the growing mass of cells. [45]. Many tumors broaden a critically hypoxic microenvironment and secrete angiogenesis-stimulating elements such set off platelet-derived increase aspect and VEGF [46]. In tumors, VEGF expression is enhanced in zones surrounding necrotic foci, suggesting a mechanism by way of which a hypoxic micro- environment may stimulate tumor angiogenesis [47]. By activation of the hypoxia-inducible aspect (HIF) family of genes, which cod for heterodimeric fundamental

helix-loop-helix proteins composed of  $\alpha$  and  $\beta$  subunits. HIF-1 $\alpha$  is synthesized inside the cytoplasm of cells but is swiftly degraded below normoxia, however, the intracellular content of HIF-1 $\alpha$  increases straight away after a lower in oxygen anxiety [48]. HIF-1 is a transcription component that mediates hypoxia caused responses [Figure 3], consisting of apoptosis and VEGF gene [49]. Hence; the oxygen availability is an essential regulator of tumor angiogenesis [50].



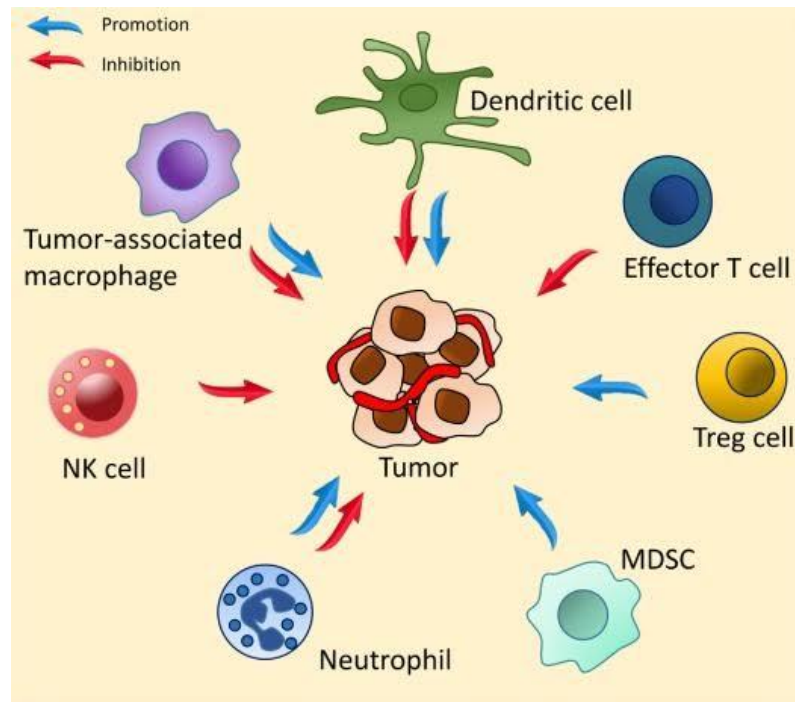
**Figure 3:** Role of hypoxia in cancer, Image adopted from Trends in Cancer; Rankin EB *et.al*, 2016 [50].

**T-LYMPHOCYTES:** CTLs offer effective antitumor immunity in host. CTLs may additionally carry out a surveillance characteristic by using spotting and killing doubtlessly malignant cells that express peptides which might be derived from mutant mobile or oncogenic viral proteins which are presented in affiliation with class I MHC molecules [51]. Role of NK cells and macrophages NK cells can be activated through direct recognition of tumor or on account of cytokines produced by way of tumor-particular T lymphocytes [52]. Recognition of tumor cells by means of NK cells is not MCH constrained [53]. In some cases, Fc receptors on NK cells can bind to antibody-covered tumor cells main to antibody dependent mobile

cytotoxicity (ADCC) [54]. By releasing lysosomal enzymes or reactive oxygen metabolites, activated macrophages play an important role in immune responses to tumors. [55]. Macrophages additionally specific Fc receptors permitting them to mediate ADCC [56]. Activated macrophages secrete TNF- $\alpha$  that has powerful antitumor interest [57]. Role of immune device in tumor improvement- immune surveillance Host affords both humoral and cellular mediated immune responses to tumor antigens and tested to be effective inside the immune destruction of tumors [58]. A range of tumors have been shown to induce tumor-unique cytotoxic -T lymphocytes (CTLs) [59]. The essential effectors consist of natural killer cells, macrophages and tumor unique antibodies [60]. T-Lymphocytes CTLs provide effective anti-tumor immunity in host [61]. CTLs may additionally perform a surveillance characteristic through spotting and killing probably malignant cells that specific peptides that are derived from mutant cell or oncogenic viral proteins which can be offered in association with elegance I MHC molecules [62].

**ROLE OF NK CELLS AND MACROPHAGES:** NK cells can be activated through direct popularity of tumor or as a result of cytokines produced by means of tumor-unique T-lymphocytes [63]. Recognition of tumor cells by way of NK cells isn't MCH restricted [64]. In some instances, Fc receptors on NK cells can bind to antibody-covered tumor cells leading to antibody based cellular cytotoxicity [65]. Numerous observations imply that activated macrophages additionally play a considerable function in the immune responses to tumors via releasing lysosomal enzymes, reactive oxygen metabolites or by means of producing TNF- $\alpha$  [66]. Macrophages also specific Fc receptors enabling them to mediate ADCC [67]. Activated macrophages secrete TNF- $\alpha$  that has potent antitumor pastime [68].

**ADCC:** In Antibody Dependent Cell Cytotoxicity (ADCC), the tumor cells, which might be coated with 1gG antibodies, are selectively lysed by using killer cells, a unique sort of lymphomonocytic cellular [69]. Several one-of-a-kind leukocyte populations like neutrophils, eosinophils, mononuclear phagocytes and NK cells are able to lysing the target cells [70]. Recognition of certain antibody takes place through a low affinity receptor for Fc $\gamma$  on the leukocyte, referred to as Fc $\gamma$ RIII or CD16 [71]. The antibody molecule presents the specific popularity signal whilst the in any other case quiescent and nonspecific effector cells are directed to the goal cells to offer the cytotoxic occasion [72].



**Figure 4:** Role of immune cells in promotion and inhibition of cancer, Image adopted from Le QV et.al., 2019 [73].

**TUMOR ESCAPE MECHANISM:** Malignant tumors may also specific protein antigens, that are diagnosed as overseas by way of the tumor host, and even though immunosurveillance may also restrict the outgrowth of some tumors [Figure 4], it is clean that the immune gadget frequently does no longer save you the incidence of human deadly cancers [73]. It can be because of the rapid growth and spread of a tumor overwhelms the effector mechanism of the immune responses [74]. The lack of ability of the host to expand an effective immune reaction has additionally been proven in several classes [75]. The method of tumor breaks out may be a result of numerous mechanisms as given below [76]. A) Class I MHC expression can be down regulated on tumor cells, that is required for CTL recognition [77]. B) Tumor products might also suppress antitumor immune responses (eg, TGF-P) [78, 79]. C) Loss of expression of tumor antigens [80]. D) Tumor surface antigens can be hidden from the immune machine [81].

**CYTOKINES:** Cytokines are small secreted proteins which mediate and regulate immunity, infection, and hematopoiesis [82]. They are small, structural proteins with molecular weights starting from 8 KD to forty KD [83]. They act via binding to unique membrane receptors, which then sign the cellular via 2nd messengers, regularly tyrosine kinases, to regulate its conduct (gene expression) [84]. Responses to cytokines include growing or reducing expression of membrane proteins (along with cytokine receptors), proliferation, and secretion



of effector molecules [85]. Cytokines are endogenous immunostimulatory proteins [86]. Cytokines play a critical position in tumor metastasis [87]. Some of the cytokines may additionally inhibit tumor increase through interfering with host tumor dating for example by means of inhibiting tumor angiogenesis and modulation of greater cellular matrix [88].

**CONCLUSION:** In maximum instances, physiological cellular dying happens via apoptosis in preference to necrosis. Abnormalities in this technique are implicated as cause or contributing thing in a variety of diseases. Inhibition of apoptosis can promote neoplastic transformation, mainly in mixture with disregulated cellular cycle manipulate, and may have an impact on the reaction to tumor cells to anti-cancer therapy. Diverse regulators of the caspases, inclusive of activators and inhibitors of mobile loss of life proteases are also observed. It is an important procedure in controlling tissue homeostasis in multicellular organisms. Apoptosis is occasionally called programmed cellular loss of life (PCD) due to the fact it is a crucial part of the developmental software and is frequently the cease end result of temporal direction of cell occasions. Apoptosis may be caused with the aid of a variety of stimuli together with ionizing radiations, gluco-corticoids chemotherapeutic dealers, lymphokines deprivation and diverse oxidants. Although the stimuli which set off apoptosis range markedly, the morphological functions of the manner are but conserved in special mobile sorts. It includes chromatin condensation, nuclear fragmentation, Plasma membrane blebbing, mobile shrinkage and formation of apoptotic bodies.

## **REFERENCES:**

1. Loeb LA, Loeb KR, Anderson JP. Multiple mutations and cancer. Proceedings of the National Academy of Sciences. 2003;100(3):776-81.
2. Khansari N, Shakiba Y, Mahmoudi M. Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer. Recent patents on inflammation & allergy drug discovery. 2009;3(1):73-80.
3. Belpomme D, Irigaray P, Hardell L, Clapp R, Montagnier L, Epstein S, Saso AJ. The multitude and diversity of environmental carcinogens. Environmental research. 2007;105(3):414-29.
4. Groeger AL, Freeman BA. Signaling actions of electrophiles: anti-inflammatory therapeutic candidates. Molecular interventions. 2010;10(1):39.



5. Verougstraete V, Lison D, Hotz P. Cadmium, lung and prostate cancer: a systematic review of recent epidemiological data. *Journal of Toxicology and Environmental Health, Part B*. 2003;6(3):227-56.
6. Dahlmann HA, Vaidyanathan VG, Sturla SJ. Investigating the biochemical impact of DNA damage with structure-based probes: abasic sites, photodimers, alkylation adducts, and oxidative lesions. *Biochemistry*. 2009;48(40):9347-59.
7. Butel JS. Viral carcinogenesis: revelation of molecular mechanisms and etiology of human disease. *Carcinogenesis*. 2000;21(3):405-26.
8. Vemuri PK, Nimmagadda G, Bodiga S, Bodiga VL, Veeravilli S, Rao KS. Immune surveillance of tumor milieu during angiogenesis. *Int. J. Life Sci. Pharma Res*. 2021;11(1):102-6.
9. Golemis EA, Scheet P, Beck TN, Scolnick EM, Hunter DJ, Hawk E, Hopkins N. Molecular mechanisms of the preventable causes of cancer in the United States. *Genes & development*. 2018;32(13-14):868-902.
10. Stamenkovic I. Extracellular matrix remodelling: the role of matrix metalloproteinases. *The journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland*. 2003;200(4):448-64.
11. Mastroianni CM, Liuzzi GM. Matrix metalloproteinase dysregulation in HIV infection: implications for therapeutic strategies. *Trends in molecular medicine*. 2007;13(11):449-59.
12. Curran S, Dundas SR, Buxton J, Leeman MF, Ramsay R, Murray GI. Matrix metalloproteinase/tissue inhibitors of matrix metalloproteinase phenotype identifies poor prognosis colorectal cancers. *Clinical cancer research*. 2004;10(24):8229-34.
13. Karalaki M, Fili S, Philippou A, Koutsilieris M. Muscle regeneration: cellular and molecular events. *In vivo*. 2009;23(5):779-96.
14. Rathna R, Madhumitha B, Viveka R, Nakkeeran E. Recent Insights of Matrix Metalloproteinase Inhibitors in Therapeutic Applications. *Enzyme Inhibition-Environmental and Biomedical Applications*. 2020;1:73-96.

15. Leeman MF, Curran S, Murray GI. New insights into the roles of matrix metalloproteinases in colorectal cancer development and progression. *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland*. 2003;201(4):528-34.
16. Johnatty RN, Taub DD, Reeder SP, Turcovski-Corrales SM, Cottam DW, Stephenson TJ, Rees RC. Cytokine and chemokine regulation of proMMP-9 and TIMP-1 production by human peripheral blood lymphocytes. *The Journal of Immunology*. 1997;158(5):2327-33.
17. Adachi Y, Nojima M, Mori M, Yamashita K, Yamano H, Endo T, Kato Y, Nakase H, Imai K, Sakata K, Tamakoshi A. Tumor Marker Publication. *Tumor Biology*. 2017;1:21.
18. Eble JA, Niland S. The extracellular matrix of blood vessels. *Current pharmaceutical design*. 2009;15(12):1385-400.
19. Xu T, Yu S, Zhang J, Wu S. Dysregulated tumor-associated macrophages in carcinogenesis, progression and targeted therapy of gynecological and breast cancers. *Journal of hematology & oncology*. 2021;14(1):1-20.
20. Feldman AL, Stetler-Stevenson WG, Costouros NG, Knezevic V, Baibakov G, Alexander HR, Lorang D, Hewitt SM, Seo DW, Miller MS, O'Connor S. Modulation of tumor-host interactions, angiogenesis, and tumor growth by tissue inhibitor of metalloproteinase 2 via a novel mechanism. *Cancer research*. 2004;64(13):4481-6.
21. Shishir TA, Khan RI, Nirzhor SS. The critical role of tumor microenvironment in cancer evolution and metastasis. *Int. J. Bus. Res.* 2018;9:244-58.
22. Stetler-Stevenson WG, Seo DW. TIMP-2: an endogenous inhibitor of angiogenesis. *Trends in molecular medicine*. 2005;11(3):97-103.
23. Wesolowski SR, Allan MF, Nielsen MK, Pomp D. Evaluation of hypothalamic gene expression in mice divergently selected for heat loss. *Physiological genomics*. 2003;13(2):129-37.
24. Carmeliet P. Angiogenesis in health and disease. *Nature medicine*. 2003;9(6):653-60.
25. Tecklenborg J, Clayton D, Siebert S, Coley SM. The role of the immune system in kidney disease. *Clinical & Experimental Immunology*. 2018;192(2):142-50.

26. Modi U, Makwana P, Vasita R. Molecular insights of metastasis and cancer progression derived using 3D cancer spheroid co-culture in vitro platform. *Critical reviews in oncology/hematology*. 2021;168:103511.
27. Keefe AD, Pai S, Ellington A. Aptamers as therapeutics. *Nature reviews Drug discovery*. 2010;9(7):537-50.
28. Weis SM, Cheresh DA. Tumor angiogenesis: molecular pathways and therapeutic targets. *Nature medicine*. 2011;17(11):1359-70.
29. Murphy DA, Makonnen S, Lassoued W, Feldman MD, Carter C, Lee WM. Inhibition of tumor endothelial ERK activation, angiogenesis, and tumor growth by sorafenib (BAY43-9006). *The American journal of pathology*. 2006;169(5):1875-85.
30. Grazul-Bilska AT, Johnson ML, Bilski JJ, Redmer DA, Reynolds LP, Abdullah A, Abdullah KM. Wound healing: the role of growth factors. *Drugs Today (Barc)*. 2003;39(10):787-800.
31. Maxwell PH, Pugh CW, Ratcliffe PJ. Activation of the HIF pathway in cancer. *Current opinion in genetics & development*. 2001;11(3):293-9.
32. Pakravan K, Babashah S, Sadeghizadeh M, Mowla SJ, Mossahebi-Mohammadi M, Ataei F, Dana N, Javan M. MicroRNA-100 shuttled by mesenchymal stem cell-derived exosomes suppresses in vitro angiogenesis through modulating the mTOR/HIF-1 $\alpha$ /VEGF signaling axis in breast cancer cells. *Cellular oncology*. 2017;40(5):457-70.
33. Sica A, Allavena P, Mantovani A. Cancer related inflammation: the macrophage connection. *Cancer letters*. 2008 Aug 28;267(2):204-15.
34. Ngo DT, Farb MG, Kikuchi R, Karki S, Tiwari S, Bigornia SJ, Bates DO, LaValley MP, Hamburg NM, Vita JA, Hess DT. Antiangiogenic actions of vascular endothelial growth factor-A165b, an inhibitory isoform of vascular endothelial growth factor-A, in human obesity. *Circulation*. 2014;130(13):1072-80.
35. Kumar VP, Prasanthi S, Lakshmi VR, Santosh MS. Cancer vaccines: a promising role in cancer therapy. *Acad J Cancer Res*. 2010;3(2):16-21.
36. Song Q, Merajver SD, Li JZ. Cancer classification in the genomic era: five contemporary problems. *Human genomics*. 2015;9(1):1-8.

37. Bi WL, Hosny A, Schabath MB, Giger ML, Birkbak NJ, Mehrtash A, Allison T, Arnaout O, Abbosh C, Dunn IF, Mak RH. Artificial intelligence in cancer imaging: clinical challenges and applications. *CA: a cancer journal for clinicians*. 2019;69(2):127-57.
38. Banerjee S, Dowsett M, Ashworth A, Martin LA. Mechanisms of disease: angiogenesis and the management of breast cancer. *Nature clinical practice Oncology*. 2007;4(9):536-50.
39. Borre M, Nerstrøm B, Overgaard J. Association between immunohistochemical expression of vascular endothelial growth factor (VEGF), VEGF-expressing neuroendocrine-differentiated tumor cells, and outcome in prostate cancer patients subjected to watchful waiting. *Clinical Cancer Research*. 2000;6(5):1882-90.
40. Funasaka T, Raz A, Nangia-Makker P. Galectin-3 in angiogenesis and metastasis. *Glycobiology*. 2014;24(10):886-91.
41. Takahashi H, Shibuya M. The vascular endothelial growth factor (VEGF)/VEGF receptor system and its role under physiological and pathological conditions. *Clinical science*. 2005;109(3):227-41.
42. Hoeben AN, Landuyt B, Highley MS, Wildiers H, Van Oosterom AT, De Bruijn EA. Vascular endothelial growth factor and angiogenesis. *Pharmacological reviews*. 2004;56(4):549-80.
43. John A, Tuszynski G. The role of matrix metalloproteinases in tumor angiogenesis and tumor metastasis. *Pathology oncology research*. 2001;7(1):14-23.
44. Devy L, Huang L, Naa L, Yanamandra N, Pieters H, Frans N, Chang E, Tao Q, Vanhove M, Lejeune A, van Gool R. Selective inhibition of matrix metalloproteinase-14 blocks tumor growth, invasion, and angiogenesis. *Cancer research*. 2009;69(4):1517-26.
45. Semaan A, Munkarah AR, Arabi H, Bandyopadhyay S, Seward S, Kumar S, Qazi A, Hussein Y, Morris RT, Ali-Fehmi R. Expression of GLUT-1 in epithelial ovarian carcinoma: correlation with tumor cell proliferation, angiogenesis, survival and ability to predict optimal cytoreduction. *Gynecologic oncology*. 2011;121(1):181-6.
46. Rajabi S, Dehghan MH, Dastmalchi R, Mashayekhi FJ, Salami S, Hedayati M. The roles and role-players in thyroid cancer angiogenesis. *Endocrine journal*. 2019;66(4):277-93.

47. Li S, Xu HX, Wu CT, Wang WQ, Jin W, Gao HL, Li H, Zhang SR, Xu JZ, Qi ZH, Ni QX. Angiogenesis in pancreatic cancer: current research status and clinical implications. *Angiogenesis*. 2019;22(1):15-36.
48. Brat DJ, Van Meir EG. Vaso-occlusive and prothrombotic mechanisms associated with tumor hypoxia, necrosis, and accelerated growth in glioblastoma. *Laboratory investigation*. 2004;84(4):397-405.
49. Semenza GL. HIF-1 mediates metabolic responses to intratumoral hypoxia and oncogenic mutations. *The Journal of clinical investigation*. 2013 Sep 3;123(9):3664-71.
50. Rankin EB, Nam JM, Giaccia AJ. Hypoxia: signaling the metastatic cascade. *Trends in cancer*. 2016;2(6):295-304.
51. Pugh CW, Ratcliffe PJ. Regulation of angiogenesis by hypoxia: role of the HIF system. *Nature medicine*. 2003;9(6):677-84.
52. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *cell*. 2011;144(5):646-74.
53. Qin M, Wang D, Fang Y, Zheng Z, Liu X, Wu F, Wang L, Li X, Hui B, Ma S, Tang W. Current Perspectives on B Lymphocytes in the Immunobiology of Hepatocellular Carcinoma. *Frontiers in Oncology*. 2021;11.
54. Senthil P, Balakrishnan H. The Engineering of Natural Killer Cells as an Emerging Adoptive Cancer Immunotherapy. *Journal of Young Investigators*. 2020;38(5).
55. Nishikawa M. Reactive oxygen species in tumor metastasis. *Cancer letters*. 2008;266(1):53-9.
56. Al-Sarireh B, Eremin O. Tumour-associated macrophages (TAMS): disordered function, immune suppression and progressive tumour growth. *Journal of the Royal College of Surgeons of Edinburgh*. 2000;45(1).
57. Gordan S, Biburger M, Nimmerjahn F. bIgG time for large eaters: monocytes and macrophages as effector and target cells of antibody-mediated immune activation and repression. *Immunological reviews*. 2015;268(1):52-65.

58. Schirmacher V, Bai L, Umansky V, Yu LI, Xing YO, Qian ZH. Newcastle disease virus activates macrophages for anti-tumor activity. *International journal of oncology*. 2000;16(2):363-436.
59. Bolhassani A, Safaiyan S, Rafati S. Improvement of different vaccine delivery systems for cancer therapy. *Molecular cancer*. 2011;10(1):1-2.
60. Souza-Fonseca-Guimaraes F, Cursons J, Huntington ND. The emergence of natural killer cells as a major target in cancer immunotherapy. *Trends in immunology*. 2019;40(2):142-58.
61. Lull C, Wichers HJ, Savelkoul HF. Antiinflammatory and immunomodulating properties of fungal metabolites. *Mediators of inflammation*. 2005(2):63-80.
62. Rodriguez GM, Bobbala D, Serrano D, Mayhue M, Champagne A, Saucier C, Steimle V, Kufer TA, Menendez A, Ramanathan S, Ilangumaran S. NLRC5 elicits antitumor immunity by enhancing processing and presentation of tumor antigens to CD8<sup>+</sup> T lymphocytes. *Oncoimmunology*. 2016;5(6):e1151593.
63. Shoshan SH, Admon A. MHC-bound antigens and proteomics for novel target discovery. *Pharmacogenomics*. 2004;5(7):845-59.
64. Zeng G. MHC class II-restricted tumor antigens recognized by CD4<sup>+</sup> T cells: New strategies for cancer vaccine design. *Journal of Immunotherapy*. 2001;24(3):195-204.
65. Erdei A, Sándor N, Mácsik-Valent B, Lukácsi S, Kremlitzka M, Bajtay Z. The versatile functions of complement C3-derived ligands. *Immunological reviews*. 2016;274(1):127-40.
66. Wagner AK, Alici E, Lowdell MW. Characterization of human natural killer cells for therapeutic use. *Cytotherapy*. 2019;21(3):315-26.
67. Harijith A, Ebenezer DL, Natarajan V. Reactive oxygen species at the crossroads of inflammasome and inflammation. *Frontiers in physiology*. 2014;5:352.
68. El Bakkouri K, Descamps F, De Filette M, Smet A, Festjens E, Birkett A, Van Rooijen N, Verbeek S, Fiers W, Saelens X. Universal vaccine based on ectodomain of matrix protein 2 of influenza A: Fc receptors and alveolar macrophages mediate protection. *The Journal of Immunology*. 2011;186(2):1022-31.

69. Weiner LM, Surana R, Wang S. Monoclonal antibodies: versatile platforms for cancer immunotherapy. *Nature Reviews Immunology*. 2010;10(5):317-27.
70. Moga E, Alvarez E, Cantó E, Vidal S, Rodríguez-Sánchez JL, Sierra J, Briones J. NK cells stimulated with IL-15 or CpG ODN enhance rituximab-dependent cellular cytotoxicity against B-cell lymphoma. *Experimental hematology*. 2008;36(1):69-77.
71. Dransfield I, Buckle AM, Savill JS, McDowall A, Haslett C, Hogg N. Neutrophil apoptosis is associated with a reduction in CD16 (Fc gamma RIII) expression. *The Journal of Immunology*. 1994;153(3):1254-63.
72. Sulica A, Morel R, Metes D, Herberman RB. Ig-binding receptors on human NK cells as effector and regulatory surface molecules. *International reviews of immunology*. 2001;20(3-4):371-414.
73. Le QV, Yang G, Wu Y, Jang HW, Shokouhimehr M, Oh YK. Nanomaterials for modulating innate immune cells in cancer immunotherapy. *Asian journal of pharmaceutical sciences*. 2019;14(1):16-29.
74. Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. *Immunity*. 2013;39(1):74-88.
75. Kumar V, Gabrilovich DI. Hypoxia-inducible factors in regulation of immune responses in tumour microenvironment. *Immunology*. 2014;143(4):512-9.
76. Gellatly SL, Hancock RE. *Pseudomonas aeruginosa*: new insights into pathogenesis and host defenses. *Pathogens and disease*. 2013;67(3):159-73.
77. Stephens PJ, Greenman CD, Fu B, Yang F, Bignell GR, Mudie LJ, Pleasance ED, Lau KW, Beare D, Stebbings LA, McLaren S. Massive genomic rearrangement acquired in a single catastrophic event during cancer development. *cell*. 2011;144(1):27-40.
78. Garcia-Lora A, Algarra I, Garrido F. MHC class I antigens, immune surveillance, and tumor immune escape. *Journal of cellular physiology*. 2003;195(3):346-55.
79. Mulligan JK, Young MR. Tumors induce the formation of suppressor endothelial cells in vivo. *Cancer immunology, immunotherapy*. 2010 Feb 1;59(2):267.



80. DuPage M, Mazumdar C, Schmidt LM, Cheung AF, Jacks T. Expression of tumour-specific antigens underlies cancer immunoediting. *Nature*. 2012;482(7385):405-9.
81. Bloy N, Garcia P, Laumont CM, Pitt JM, Sistigu A, Stoll G, Yamazaki T, Bonneil E, Buqué A, Humeau J, Drijfhout JW. Immunogenic stress and death of cancer cells: contribution of antigenicity vs adjuvanticity to immunosurveillance. *Immunological reviews*. 2017;280(1):165-74.
82. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. *Frontiers in immunology*. 2014;5:491.
83. Zhao JL, Ma C, O'Connell RM, Mehta A, DiLoreto R, Heath JR, Baltimore D. Conversion of danger signals into cytokine signals by hematopoietic stem and progenitor cells for regulation of stress-induced hematopoiesis. *Cell stem cell*. 2014;14(4):445-59.
84. Ryan SM, Mantovani G, Wang X, Haddleton DM, Brayden DJ. Advances in PEGylation of important biotech molecules: delivery aspects. *Expert opinion on drug delivery*. 2008;5(4):371-83.
85. Chao MV. Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nature Reviews Neuroscience*. 2003;4(4):299-309.
86. Robertson CA, Evans DH, Abrahamse H. Photodynamic therapy (PDT): a short review on cellular mechanisms and cancer research applications for PDT. *Journal of Photochemistry and Photobiology B: Biology*. 2009;96(1):1-8.
87. Guillot L, Balloy V, McCormack FX, Golenbock DT, Chignard M, Si-Tahar M. Cutting edge: the immunostimulatory activity of the lung surfactant protein-A involves Toll-like receptor 4. *The Journal of Immunology*. 2002;168(12):5989-92.
88. Bussard KM, Gay CV, Mastro AM. The bone microenvironment in metastasis; what is special about bone?. *Cancer and Metastasis Reviews*. 2008;27(1):41-55.
89. Griffioen AW, Molema G. Angiogenesis: potentials for pharmacologic intervention in the treatment of cancer, cardiovascular diseases, and chronic inflammation. *Pharmacological reviews*. 2000;52(2):237-68.