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TUMOR MICROENVIRONMENT- A REVIEW

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Abstract:

Cancer is a complex entity with multiple components affecting a tumor growth, invasion and metastasis. Traditionally cancer treatments have focused on tumor cells. Microenvironment also has role in tumor behavior. Biological agents that target components of the tumor microenvironment may provide an alternative to traditional therapy. Because of the complexity of the tumor milieu the most beneficial therapy will likely involve the combination of one or more agents directed at the microenvironment.

Keywords: Tumor, Microenvironment, Metastasis, Extra cellular matrix.

Introduction:

Tumors are complex structures containing different cells. Microenvironment is the interface between the tumor cells and the normal stromal cells. [1] A tumor stimulates the remodeling of its microenvironment for its own survival. The tumor changes the structure of the extracellular matrix for its own growth, induce angiogenesis and alter the function of existing cells .[2]

The tumor microenvironment represents a new altered condition favorable for the tumor to progess.[3] Components of tumors including resident non cancer cells like fibroblasts, endothelial cells, connective tissue and extracellular matrix containing proteins like collagen are equally important both in tumor initiation and progression. The stroma is considered important for the tumor cells to survive and grow as they are the source of oxygen and nutrient supply.

Tumor Microenvironment Components:

The tumor microenvironment consists of cancer cells, non-cancer cells, secreted soluble factors and non-cellular solid material. The tumor microenvironment is highly variable. Solid malignant tumors are basically composed of neoplastic cells collectively called parenchyma and non-tumors elements, the stroma. [4,5]

1. Cancer Cells :

Cancer cells differ from normal cells by its growth, differentiation, altered replicative potential and invasiveness.

a. Cancer Cell Survival

The cancer cells shows metabolic alteration such as increased glycolysis and altered mitochondrial respiration which uses the glycolysis f or Adenosine triphosphate (ATP) supply.

This led to accumulation of Nicotinamide adenine dinucleotide phosphate (NADP) that leads to inactivation of Phosphatase and tensin homolog (**PTEN**) and activation of prokinase B (Akt). The cancer cells have mitochondrial DNA mutations and hypoxia which increases glycolysis and activation of Akt pathway through nicotinamide adenine dinucleotide hydride(NADH) mediated PTEN inactivation is important in its survival.[6]

b. Cancer Cell Growth

As cancer cells replicate so fast, they often show a multinucleated phenotype and contain numerous nuclei which is abnormal in its shape and size. The molecular analysis of human tumor has shown that cell cycle regulation is frequently mutated in human tumors. The critical point of cell cycle control is the restriction point. The restriction point is controlled by the cyclin D and cyclin E

dependent kinases. Tumorigenesis is frequently associated with mutations or abnormalities in the expression of various cyclin, Cyclin-dependent kinases CDK's and CKI's.[7]

C. Cancer Initiating Cells

Virchow in 1955 was proposed that embryonic remnants in adults were the cancer initiating cells. Cancer initiating cells are self-sustaining cells with the exclusive ability to self-renew. The cancer initiating cell niche is made up of stromal initiating elements. The niche maintains stem cells and cancer initiating cells by secreting factors, providing cell – cell contact and regulating micro-environment. The epigenetic changes and genetic mutation can provoke the stem cells residing in adult tissues give rise to cancer .Tissue stem cells are ideal targets for oncogenesis. Not all cancers arise from a tissue stem cell. The cancer initiating cells can also arise from progenitor cells which lack the ability to self-renew. [8]

2. NON CANCER CELLS :

A number of non-neoplastic cells help comprise the tumor microenvironment. These include cancer associated fibroblast, tumor endothelial cells, pericytes, bone marrow progenitor cells and a number of immune cells including tumor associated macrophages. These cells may increase or suppress metastasis by availability of pro and anti-metastatic factors. [9]

a. Cancer Associated Fibroblasts (CAF):

In malignant tumors, fibroblasts and myofibroblasts form the main stromal component. Tumor associated fibroblasts differ from their normal counterpart in many ways .The histology and growth characteristics of carcinoma associated fibroblasts differ from those of fibroblasts associated with normal epithelial cells and several altered properties by increased collagen production and stimulation of hyaluronate synthesis in fibroblasts.

Fibroblast activation protein (FAP), a 97kDa surface glycoprotein, is over expressed in a majority of cancer related fibroblasts and it was shown to promote tumor growth. Greater level of FAP in patients with metastases was associated with a shorter survival. The cells of the immune system are also influenced by the tumor associated fibroblasts. [10]

Metallothionin is a protein responsible for modulating the immune system cells by their anti-apoptotic and pro proliferative properties. The expression of this protein by the fibroblasts of the tumor microenvironment is related to the remodeled phenotype of these cells because of the tumor influence on cancer associated fibroblasts. [11]

Myofibroblast produce a large amount of stroma cells derived factor -1 (SDF-1) promoting tumor growth and metastatic spread. These cells also secrete Insulin-like growth factor 1 (IGF-1), hepatocyte growth factor HGF, vascular endothelial growth factor VEGF, interleukin -6 (IL-6), all these compounds result in a significant increase of the invasive capacity of tumor cells [20]. Myofibroblast are highly proliferative and are surrounded by a dense meshwork of the structural protein collagen. [12]

Tumor associated fibroblasts also supply a variety of cytokines, growth factors, tissue-remodeling enzymes and ECM components, all of which modulate host-tumor interactions. The origin of tumor associated fibroblasts, myofibroblasts is still an unsettled issue. [13]

b. Tumor associated macrophages (TAM):

They are bone marrow derived cells capable of influencing tumor invasion, angiogenesis, immune evasion and migratory behavior. Sub populations of TAM's may alter both spatially and temporarily during tumor development to orchestrate malignant progression. Cytokine-mediated monocyte differentiation can produce dichotomous effects.

Suppressor M_1 macrophages, secreting mediators such as TNF α, IL-12 produce a pro-inflammatory effect which promotes the host anti-tumor immune response. M_2 promoter macrophages, expressing anti-inflammatory cytokines such as IL-10, TGF β, VEGF act to enhance tumor growth invasion and angiogenesis and subvert the host immune response to tumor antigens .[14]

TAM's produce high levels of Hypoxia inducible factor -2α (HIF-2α) and this is an independent prognostic factor for poor outcome. They impaired phagocytic activity by producing much less nitric oxide than the normal monocytes. The toxic compounds released are Tumor necrotic Factor α, Nitric Oxide, H_2O_2, proteases, immunosuppressive materials,

various growth factors and cytokines that results in increased mitotic activity, promoted invasiveness and enhanced neo angiogenesis .[15] The ability of TAM's to stick to tumor cells allows macrophages to carry tumor cells in to the circulation and thus aid in the spread of the cancer.

c. Pericytes:

A pericyte is also known as Rouget cell adventitial cell or mural cell in a connective tissue that occurs in the small blood vessels.[16] Pericytes are critical for angiogenesis, new vessel formation within the body of a tumor. PDGF-β over expression within tumor results in increased pericyte coverage.During vascular development these progenitor cells of pericytes can be recruited through, SDF-1α chemo taxis gradient and differentiate into VSML and or pericytes to facilitate the blood vessel formation. [17]

d. Bone Marrow Progenitor Cells:

Bone marrow derived Endothelial Progenitor Cells (EPC) is present in the peripheral blood and increased in response to certain signals and seen in the neo vascular bed of malignant tissues. Bone marrow serves as a source for the needed progenitor cells as the tumor vasculature expands during tumor growth. These cells are not distributing homogenously throughout the tumor.[18]

e. Adipocytes:

These are cells that primarily constitute adipose tissue which secretes several specific cytokines like adipokines, leptin, adiponectin, resistin and visfatin and stores energy as fat. Adipose tissue secretes metalloproteinases which influence inflammation and angiogenesis in tumor .[19]

3. SECRETED SOLUABLE FACTORS:

In addition to the cellular compartment an array of secreted soluble factors regulates tumor metastasis. These factors can both stimulate or inhibit tumor metastasis.

a. Chemokines:

Chemokines are known to modulate a number of processes important to tumor metastasis including stimulating the migration and infiltration of immune cells such as macrophages, T cells, dendritic cells and natural killer cells. Certain Chemokines play roles in directing migration of tumor cell to specific metastatic sites. These molecules have both pro and anti-metastatic activities. [20] CCL_2 CCL_5(Chemokine C-C motif ligand) suppression of malignancy by stimulating immune function and infiltration of T cells and natural killer cells to the sites of tumor growth.CXCL12 /SDF-1 – play a role in facilitating tumor cell migration and homing to distinct metastatic sites, while others help stimulate angiogenesis $CXCR_3$ – Immuno-angiostatic property. CXCL10 – Promotes the proliferation of CXCR3, expressing tumor cells and to stimulate their adhesive and invasive properties .[21]

b. **Matrix Metalloproteinase** (MMP):

The matrix degradation is mediated by the concerted action of several proteinases, including members of the serine, cysteine, aspartate and MMP families. Majority of the connective tissue destruction is carried out by the MMP's, a zinc dependent enzyme that degrades all components of the connective tissue. .MMP's can contribute to tumor growth either through direct or indirect processing of several growth factors such as FGF, TaF-β. MMP's are also involved in the release of insulin like growth factor protein from their growth inhibitory binding proteins which stimulate tumor growth. MMP's can indirectly regulate proliferation through integrins as a consequence of their ability to allow the makeup of the ECM.MMP's also provide protective effects by suppressing tumor growth.[22]

c. Matricellular proteins

They are characterized as secreted proteins that bind cell surface receptors, ECM components and proteases but are not considered structural elements of the ECM. Examples of these molecules are thrombospondin-1 and 2 (TSP 1, 2), Secreted protein acidic rich in cysteine (SPARC) and connective tissue growth factor (CTGF). These substances can play both stimulatory and inhibitory roles in metastasis .[23]

d. Growth factors

Stromal cell derived factor-1 (SDF-1) produces an endocrine effect by recruiting circulating endothelial progenitor cells to the tumor. SDF-1 is secreted by the activated fibroblasts.

Transforming growth factor-β (TGF-β) recruits EPC to the microenvironment is involved in the activation of fibroblasts to CAF. Platelet derived growth factor (PDGF) is involved in recruiting and proliferation of fibroblast. Vascular Endothelial Growth Factor (VEGF) indirectly supports micro environmental changes via creation of dysfunctional vascularization that allows plasma leakage which attracts fibroblasts and other cells. [24]

4. NON CELLULAR SOLID MATERIAL :

Hyaluronan (HA) is present in the extra cellular microenvironment is responsible for malignant behavior of cells by cell proliferation. Excess production of Hyaluronan will enhance the tumorigenic ability in certain tumors. They link the tumor aggregate cells from the tumor micro environment with the stromal cells. This hylauronon rich microenvironment will increase the monocytes and macrophages and also the endothelial and bone marrow cells results in angiogenesis and lymph angiogenesis.[25]

METASTASIS: Metastasis can be defined as the development of secondary tumors at a distant site from the primary tumor.26 Integrin receptors is responsible for the attachment of the tumor cells to the extracellular matrices. The tumor cell migration can be dependent on many factors.

Seed and Soil Hypothesis

In 1989 Stephen Paget developed the hypothesis that certain tumor cells (seeds) can only successfully colonize selective organs (soil) that have suitable growth environments. In modern context this hypothesis would state that malignant cells (seed) gradually acquire mutations in oncogenes or tumor suppressor genes that confer the ability to egress from the tissue of origin survive in hematogenous or lymphatic circulation and proper in a distant site (soil).[27]

ANGIOGENESIS:

Tumors induce new blood vessel formation from pre-existing vessels in a process called tumor angiogenesis to obtain sufficient oxygen and nutrients for growth and survival within primary sites. Newly formed blood vessels play a pivotal role in promoting enhanced turnover metastasis to distant organs .It is an essential pre-requisite for tumor growth and metastasis. Tumors grow only up to a volume of 2-3mm^3 and stop further growing without a sufficient vascular supply. Angiogenesis activators such as vascular endothelial factor, FGF-2, Angiopoietin-1 (Ang 1), angiopoietin-2 (Ang 2) and their receptors are involved in these processes. Angiogenesis inhibitors are fibronectin, thombospondin-1, angiostatin and endostatin .[28] Tumor angiogenesis occurs by proliferation of endothelial cells and by bone marrow derived progenitor circulating endothelial cells.

LYMPHANGIOGENESIS:

The outgrowth of lymphatic vessels is lymph angiogenesis. The spread of cancer cells occurs through sentinel lymph node from the primary tumor to distant organs. Tumor can induce lymph angiogenesis in both primary tumor and lymph node via release of the lymph angiogenic growth factors, VEGF-C or VEGF-D leading to increased rates of metastasis to the draining sentinel lymph nodes and beyond. Mediators of lymph angiogenesis are FGF-2, HGF (hepatocyte growth factor / scatter factor) VEGF-C and VEGF-D. High tumor interstitial fluid pressure is thought to promote tumor cell entry into lymphatic vessels that have lower fluid pressure. Tumor associated lymph angiogenesis has potential significance in primary site and also in lymph nodes. The sinusoidal lymphatic endothelium facilitates the transport of the tumor cells to lymph nodes and helps in the survival of the cancer stem cells by a specific tumor micro environment .[29]

CONCLUSION

Tumor cells modify stroma and vasculature and the locally changed host microenvironment in turn modifies the behavior of tumor cells. Traditionally cancer treatments have focused on tumor cells. By understanding the interactions between cells of the tumor microenvironment and how these interactions affect tumor progression, we can develop better therapies involving complementary and synergistic combinations.

REFERENCES:

1. Balkwill F.R., Capasso M., Hagemann T. The tumor microenvironment at a glance. J. Cell Sci. 2012;125:5591–5596.
2. Dutsch-Wicherek M. RCAS1,MT, and Vimentin as potential markers of tumor microenvironment remodeling.AM J ReprodImmunol 2010;63:181-88

3. EzioLaconi. The evolving concept of tumor microenvironments. Bioessays 2007;29(8):738-44
4. Harriet W, Robert V and Klaus P. Cancer micrometastasis and tumor dormancy. APMIS 2008;116:754-70,
5. Ralph J. DeBerardinis. Metabolic pathways promoting cancer cell survival and growth. Nature Cell Biology 2015 ;17:351–359
6. Jiangbin Y Jeing Fan, Sriram Venneti, Ying-Wooi Wan et al. Serine catabolism regulates mitochondrial redox control during hypoxia. Cancer Discov2014; 4:1406–1417
7. Moon-Taek Park and Su-Jae Lee. Cell cycle and Cancer J Biochem and Mol. Biol. 2003;36(1):60-65.
8. E.Hanna, J Quick, SK Libutti. The tumor microenvironment: a novel target for cancer therapy. Oral Diseases 2009;15:8-17
9. Alexandra Cretu and Peter C.Brooks. Impact of the Non-Cellular tumor Microenvironment on Metastasis: Potential Therapeutic and Imaging Opportunities. J. Cell.Physiol.2007;213:391-402
10. Shiraki, N . Methionine metabolism regulates maintenance and differentiation of human pluripotent stem cells. Cell Metab.2014. 19, 780–794
11. Santos AM, Jung J, Aziz N, Kissil JL, Puré E. Targeting fibroblast activation protein inhibits tumor stromagenesis and growth in mice. J Clin Invest 2009; 119:3613 - 25;
12. Ferrara N .VEGF as a therapeutic target in cancer..Oncology. 2005;69 Suppl 3:11-6
13. Naoki I, Lisheng Z, Koji K. Impact of the hyaluronan-rich tumor microenvironment on cancer initiation and progression 2008;99(9):1720-25
14. Caroline Coghline and Graeme I Murray. Current and emerging concepts in tumor metastasis. J. Pathol 2010; 222:1-15
15. Lewis CE, Pollard JW. Distinct role of macrophages in different tumor microenvironments. Cancer Res. 2006;66(2):605–12.
16. SerenellaM.Pupa, Sylvie M, Stefania F and Elda T. New Insights into the Role of Extracellular Matrix during Tumor Onset and Progression. J. Cell. Physiol.2002;192:259-67
17. Rebecca G.Bagley, William Weber, Cecile Rouleau, and Beverly A. Teicher. Pericytes and Endothelial Precursor Cells: Cellular Interactions and Contributions to Malignancy. Cancer Res1,2005 65; 9741
18. Krishna R, Zhichao Z, Keri S, Shu-Fang Jia and Eugenie S. Bone Marrow subsets differentiate into endothelial cells and pericytes contributing to Ewing's tumor vessels.Mol Cancer Res 2008;6(6):929-36
19. Nieman KM, Romero IL, Van Houten B, Lengyel E.Adipose tissue and adipocytes support tumorigenesis and metastasis BiochimBiophysActa. 2013 ;1831(10):1533-41.
20. Nisha N , Max S Wicha , Weiping Zou. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy Nat Rev Immunol2017 Sep;17(9):559-572
21. Slettenaar VI, Wilson JL.The chemokine network: a target in cancer biology?Adv Drug Deliv Rev. 2006 Oct 1;58(8):962-74.
22. Saray Q, Rodrigo A, et al. Role of Matrix Metalloproteinases in Angiogenesis and Cancer.FrontOncol. 2019; 9: 1370.
23. Paul Bornstein Matricellular proteins: an overview.J Cell Commun Signal.2009 ; 3(3-4): 163–165.
24. Waters MJ, Brooks AJ. Growth hormone and cell growth. Endocr Dev. 2012;23:86-95
25. Csoka AB, Frost GI, Stern R The six hyaluronidase-like genes in the human and mouse genomes. Matrix Biol2001;20:499–508
26. Anne C. Chiang and Joan Massagué. Molecular Basis of Metastasis. N Engl J Med. 2008 Dec 25; 359(26): 2814–2823.
27. Panel N,Angela S, Casilda L ,Emilio A. The seed and soil hypothesis revisited: Current state of knowledge of inherited genes on prognosis in breast cancer Author links open overlay. Cancer Treatment Reviews. Volume 40, Issue 2, March 2014, Pages 293-299
28. DeryaTilki, Nerbil K, Sema S, Friedrich Z, Christian G, Suleyman E. Zone specific remodeling of tumor blood vessels affects tumor growth. Cancer 2007:110:2347-62
29. Dai F, Rakesh K. Jain. Imaging angiogenesis and the microenvironment. APMIS 116:695-715, 2008