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PROGRESSION OF CANCER : FOCUS ON METASTASIS WITH DIFFERENT ASPECTS

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ABSTRACT

The role of metastasis on the poor prognosis of cancer is undeniably important. For this reason, revealing the role of metastasis and defining the factors contributing to it play a key role in the treatment of cancer. In this review, we aimed to research various genes, markers and factors related to metastasis, the functions of platelets in metastasis, tumor's ability to dodge the immune system and two different aspects of autophagy in tumor cells. Under the prognosis section, we gave more details on epithelial-mesenchymal transition which has a role on the malignancy and we examined the effect of factors on metastasis. In other two sections, we mentioned that thrombosis and platelets support metastasis, platelets play a role in dodging immune system and there are two opposite mechanisms triggering tumor formation.

Keywords: Metastasis, epithelial-mesenchymal transition, platelet

INTRODUCTION

Cancer is a process relying on unregulated cell division. Cancer cells not only divide and multiply irregularly, but they also accumulate and form tumors. Benign tumors do not have the ability to spread to neighbor tissue and organs, and they are differentiated, meaning that they possess similar characteristics like regular cells; whereas malign tumors are expected to spread to neighbor tissues. Alongside their ability to infiltrate and damage tissues, they can also spread to some other parts of the body and form secondary cancer colonies, which are called metastasis. Revealing the causes of cancer and determining its course in early phases is recently one of the most important fields of study. Many pathways which are particular to living organisms and cannot be explained in vitro, provide ideas regarding the spread of cancer and determining its prognosis beforehand. This review aims to approach metastasis with different aspects and provide a general knowledge.

Progression Of Cancer

Tumors are able to metastasize via blood or lymph, as it is known. It is not easy to describe the metastasis with experimental methods by forming microenvironment. Metastasis is expected to show up during late phases, for this reason detecting factors which can predict early metastasis and prognosis of the disease is very important since it can affect treatment protocol and improve the survival. HER2 and PyMT have increased the spread of tumor cells by early epithelial change in transgenic mice and human ductal carcinoma (1). Cytokeratin (CK) is an epithelial marker and it is not present in bone marrow under normal conditions. In breast cancer patients, a CK (+) result provides important information about a presence of micrometastasis and shows that there is a high risk for relapse (2).

The most important factor to determine if a malignant transformation will occur is the micro environment of the tumor (3). By excreting various cytokines, the tumor activates stromal fibroblasts. Stromal cells excrete growth factors and cytokines, thus epithelial-mesenchymal transition (EMT) occurs (4). When we thoroughly examine EMT in squamous cell carcinoma, the cancer stem cells which express high level of CD44 undergo EMT with the help of stromal factors and become cancer stem cells. These cells enter the blood circulation and migrate to a secondary site; they undergo a mesenchymal-endothelial transition (MET) and join the epithelial cells, causing metastasis (5). The most important cause of EMT is exposure to TGF-ß (6). Most growth factors stimulate proliferation and trigger carcinogenesis. TGF-ß group growth hormones are a little different. TGF-ß excreted from human platelets show similar biologic characteristics with growth inhibition factor excreted from BSC-1* (Epithelial cell originated from African green monkey) cells (7, 8). An experiment done

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with transgenic mice reveals a deterioration of tumor forming mechanism with increased TGF-ß signal (9). But the fact that TGF-ß increases EMT and causes metastasis by increasing the spread in primary carcinomas is an important aspect (10). When TGF-ß antibodies were given to mice breast cancer models with a T-cell deficiency and normal natural killer (NK) cell functions, mice spleen NK activity was improved and tumor cell proliferation was regressed (11). An increase on TGF-ß induces metastasis and angiogenesis in prostate cancer, while weakening the immune system (12). TGF-ß plays an important role on cell proliferation and extracellular matrix configuration. In patients with non-metastatic primary lesion or lymph node metastasis, TGF-ß levels measured in peripheral veins and tumor draining vein is closely related to invasion and metastasis of gastric carcinoma (13).

In a research in which invasion and metastasis were analyzed by measuring IGF binding proteins, IGFBP-2 was increased in prostate cancer patients when compared to healthy individuals. However, IGFBP-3 is different. In patients whose preoperative plasma has low amounts of IGFBP-3, prostate cancer has a more aggressive course (14).

Spread Of Tumor Cells And Platelets

EMT is known to increase with an interaction between platelets and tumor cells, as well as an increase on TGF-ß (15). The main point to emphasize is the interaction of platelets with tumor cells and the effect of platelets on metastasis. In cancer patients, the risk of thrombosis increases in later stages. The reason for that is abnormal platelet activation and aggregation. Even if thrombotic disorders do not occur, coagulation parameters mostly increase. Factor VII of the extrinsic pathway and tissue factor are elevated in cancer patients (16). When we approach from another aspect, thrombocytosis is known to be related to short lifespan and aggressive disease (17). Thrombopoietin and IL-6 are known to be increased in patients with thrombocytosis, but researches done with mice show that the main cause of paraneoplastic thrombocytosis is the tumor-related increase of IL-6 (17). Anti IL-6 antibodies have reduced the amount of platelets in mice with epithelial over cancer and IL-6 blockade has increased the response to medication in epithelial over cancer (17).

Tumor cells in the blood are always in a relation with the hemostatic system. Especially platelet and tumor cells' complex interaction mechanisms must always be kept in mind. As it is known, platelets are cells without nucleus which include many granules and they derive from megakaryocyte's cytoplasm. Platelet membrane consists of phospholipids and it is surrounded by glycoprotein and integrines. Platelet membrane glycoproteins cause adhesion in subendothelial matrix, adhesion between platelets and aggregation (18). P2Y1 receptor located in the platelet membrane serves a function in ADP-dependant platelet aggregation (19). At this point, we need to stress that with adenine nucleotides excreted from ATP-activated P2Y2 receptor-controlled platelets, the endothelial barrier disappears and cancer cells can pass through the endothelium and wander outside of veins (20). In a research done with mice, it was shown that with a P2Y2 deficiency or a deficiency of ATP secretion, tumor cell metastasis decreases (21). With a relation between platelets, tumor cells and leucocytes, CCL-5 synthesis from endothelium has raised and this has increased metastasis (22).

Immune System And Autophagy

Tumor cells are able to dodge the immune system with various mechanisms. MHC1 and tumor antibodies must be presented to the cytotoxic T-cells so that they can identify and destroy cancer cells. Tumor cells can reduce the HLA1 expression and decrease anti-tumor activity (23). In multiple myeloma, with the interaction of myeloma and tumor cells and with the effect of myeloid-dependant suppressor cells, the tumor proliferation has increased and immunodeficiency has occurred (24). When myeloid-dependant suppressor cells encounter neutrophils, CD115 and CD244 expression has increased, however, CXCR1 and CXCR2 expressions have decreased (25). During hematogenous metastasis, platelets surround the tumor and let them be transported safe from the immune system (26). With this, the ability of NK cells to lyse tumor cells is disabled (26). It was shown that fibrin formation and fibrin surrounding tumor cell block the recognition of tumor cells by the NK cells and thus increase metastasis (27).

Apart from this, in our knowledge it is also necessary to mention autophagy. Autophagy is defined by the removal of damaged, unnecessary proteins and organelles with cellular degradation. In cancer, autophagy has a more complicated and difficult mechanism. In early stages of cancer development, autophagy has a tumor suppressant character. A decreased autophagy in early stage tumor cells is related to malignant transformation. Moreover, increased autophagy in cancer cells which

have already existed beforehand protect the tumor cells against metabolic and therapeutic stress and plays a role in pro-tumor mechanisms (28). In other words, chemotherapy and radiotherapy have been lethal on late stage already existing tumors, where autophagy was inhibited, and this has created treatment-sensitive cancer cells (28).

CONCLUSION

In cancer, the course of disease changes in every patient depending on various factors. Treatment protocol is determined up to date with some genes and microscopic changes in tumor, and aggressive treatment is applied in case of poor prognosis. Another important aspect is that platelets can overexpress some receptors and help the tumor to spread secondary organs outside of veins, and thus increase the metastasis. Blocking this can prevent the tumor from leaving the veins and spread to tissues. Eliminating the deficiency of immune recognition originating from an interaction between fibrin, platelets and tumor cells will improve the ability of the organism to fight the disease.

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