



The process of tumor metastasis and its influencing factors: A review

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ABSTRACT

The transfer of tumor (tumor metastasis) is composed of a series of discrete biological processes, making tumor cells from the primary tumor to the remote parts of the process. Tumor cells invade surrounding tissue, tumor (invade) primary enters lymphatic fluid or blood, in the circulatory system, can survive and remain in it, then spilled from the vascular (extravasate) to form a solid tumor proliferation in new places. This process mainly involves the interaction of tumor cells and their surrounding environment and the regulation of many kinds of factors. This paper simply introduces the occurrence, development and classification of the tumor metastasis and some factors include body tyrosine kinase Abl (Abelson kinase) on the impact of the process.

Keywords: transfer; Abl PTPRO

INTRODUCTION

Tumor metastasis, tumor metastasis, tumor cells from the primary sites invade lymphatic vessels, blood vessels, or body cavity to migrate elsewhere and continue to grow through the circulation system, the same type of tumor formation and primary tumor is a process of metastasis. So far, the study of tumor metastasis has been 100 years, as early as 1908, Le Conte RG. I found the appendix to colonic carcinoma (Ileocolic Glands) [1]. And now the tumor metastasis is still the majority of the major causes of death, but the mechanism of tumor metastasis is still not completely clear. Stephen Paget put forward the classic "seed and soil" theory to explain the mechanism of tumor metastasis, and the transfer of tumor depends on the cancer cells (so-called seeds) and particular organ microenvironment (i.e., soil) mutual recognition [2].

Involved in tumor metastasis Abl are the process of the cytoskeleton reorganization, regulating cell between gelling, flaking pseudopodia formation and tumor angiogenesis and so on. In K562 cells, the PTPROt can modify Bcr - Abl phosphorylation level to influence its function, suggesting that PTPRO may also participate in the regulation of tumor metastasis. The tumor metastasis process could further clarify the mechanism, and provide important theoretical basis for clinical treatment of tumor.

1. The process of tumor metastasis

Tumor metastasis is free cancer cells and allows the interaction between the target tissue, the process involves a better choice for cancer events and accommodate a tumor in the matrix of the tumor cell.

1.1 Transfer occurrence

Transfer occurs the strict control of behavior of the environment under the selection pressure of cells, with the evolution of the genetic diversity of cancer cells [3]. Cancer metastasis is a very inefficient process, tumor releases millions of cancer cells every day, but only a very small amount of cells can form the remote organ lesions and normal tissue have inhibitory effect on tumor cells invaded, so it need 1.1.1 Gene genomic instability

In some proto-oncogenes may spur tumor cells developed into the transfer state, these all make a genome instability,

in addition, the cause of tumor initiation mutations can lead to genomic instability. The probability of development of high metastatic tumor cells cloned gene mutation is higher.

Cancer genome instability within basically has 3 kinds of forms: DNA mutations, chromatin remodeling, and apparent change. Cell cycle, for example, inhibit protein Rb deactivation causes mitotic checkpoint regulation of Mad2 expression change, causes the genome of euploidy [3], cancer gene signal Akt activation Chk1 lost the ability of DNA damage sensor, etc. [4].

The transfer of the host part related genes Sip1 (signal-induced effort- associated gene 1), over expression promotes the shift, the polymorphism affects its Ras GTPase activating protein Ras - GTP [5]. MKK4 MSGs (metastasis suppressor genes) is a kind of MSG, p38 lightning and Jnk members of mitosis activated protein kinase pathway, MKK4 activity is caused by new environmental pressure loss of inhibition of tumor cell apoptosis, conducive the formation of metastases. [6]. BRMS1 is close to the PI3K signaling pathway, junction promotes the communication between cells through gap[7]. Nm23 inhibition of Erk pathway causes cells to stick together, affecting cell metabolism [8].

1.1.2 Environmental pressures

Environment makes tumor cells form of invasive phenotype selection pressure can be divided into the internal pressure inside the cell (intrinsic) and the external pressure (extrinsic). The former has the cells within tumor suppressor genes, proto-oncogenes, Epi/based instability caused by Genetic toxicity. While the latter can be roughly divided into three groups: (1) biological factors, such as extracellular matrix (extracellular matrix, ECM) composition, the attack of the immune system and inhibitory cytokines; (2) chemical factors, the lack of oxygen and nutrients, low pH; (3) physical factors, basement membrane (basement membranes), internal stress and tension. These are associated with the instability of the genome, and can promote the transfer of gene expression [9].

1.1.3 tumor-initiating cells (tumor-initiating cell)

In the process of embryonic development, stem cells can not symmetrical divide, producing a different ability of proliferation and differentiation of cells and stem cells. Now in leukemia [10] a few solid tumors were, such as breast cancer [11, 12], brain tumor stem cells exist in the [13] cells. Tumor may not be able to rely on a small part of the gain directional self-renewal ability of malignant cells, these tumor-initiating cells sometimes refer as the cancer stem cell (cancer stem cell). In these cell separation, you can produce all of the changes of cell phenotype, and beginning ability is one of the few surviving tumor cells in distal metastasis location reconstruction tumor entity.

Polycomb protein family is a Bmi-1 transcription inhibitory factor. Valk-Lingbeek *et al.*, found that the effect also exists in tumor initiation (leukemic stem cells) [14]. Other normal self update mechanism of genetic changes may enhance the efficiency of the transfer. Hedgehog signals, such as expression of transcription effector Gli1, can make the rat prostate cancer cells to the pulmonary metastasis [15].

1.1.4 Mirnas

The length micrnas (miRNA) is about 21 to 25 nt, it is endogenous, naturally occurring, evolution of conservative and non-coding RNA, its sequence is similar but not identical genes encoding proteins, the exercise of transcription inhibition effect. Micrnas can serve as the original oncogenes or tumor suppressor genes, influence the development of cancer and processes. Micrnas DNA methylation related silence associated with the development of human cancer and its metastasis, Worley LA and others are found in the eye of melanoma (uveal melanoma), the expression of micrnas may be a high precision of tumor metastasis biomarker [16].

1.2 Transfer of development

1.2.1 Gelling of cellular changes

In the process of malignant change, changes in cancer cells gelling properties diverse to escape the constraints of the organizational structure, promote the progress of the transfer. This change mainly involves between cancer cells and cancer cells with extracellular matrix and other adhesive.

Integrins are 18 eight alpha and beta subunits of different source which consists of a dimer, mainly to maintain cells and extracellular matrix of gelling, are also an important cancer malignant transformation of mediation. Every heterologous dimers and ECM can bind to a specific protein and in the inside cells and outside signal transmission, especially the integrin alpha beta 4 and 6 fibronectin combination of extracellular matrix, and the original cancer of receptor tyrosine kinase Met, EGFR, Her2 form signal compounds; Integrin alpha v beta 3 and alpha and beta 1 involve in the transfer process of late tumor cells in the circulation system attached to the process of blood vessel walls [17, 18].

1.2.2 Attacks to basement membrane and extracellular matrix (night)

Attacks (night), are a start of shift process, cadherin express attacks tumor cells, tumor cells and cells and extracellular matrix (extracellular matrix, ECM) gelling, cell movement ability change, protease degradation of surrounding tissue and cells of motility promoting itself through the organization. Cell movement ability promote cell migration is a dynamic process, the molecular level is involved in the dynamic changes of the cytoskeleton, cell-matrix interaction, partial hydrolysis of protein, actin and myosin contraction and focal contract decomposition. Control nodes include: small GTPases (Rho, cdc42 and Rac), containing assembly of gelling spot of the integrin reconciliation, protease within the scope of the potential and the plasma membrane excited globulin contraction and equipment.

Cell invasion: Growth factors directly or indirectly involve in the process. Nedd9 is a gelling spot kinase receptor proteins, the copy number increases and expresses, promoting cells to move and attack, can also be mediated by the pulmonary metastasis of breast cancer. Gelling element of transmembrane glycoprotein Podoplanin in many malignant tumors, hit the front of the expression in the presence of E-cadherin enhance cells, presumed by adjusting the cytoskeleton anchor protein Ezrin [19,20,21].

Another form of attack-ameboid is due to loose contact with the extracellular matrix and cell polarity, the boundaries of the shape of the cells and tissue cells with minimal resistance for rapid movement.

Cells to survive: in the process of transfer, tumor cells must also avoid dying in microenvironment of stimulus signal, such as the lack of oxygen and nutrients, extracellular adhesive, cell shape, the change of the stromal microenvironment can cause cell death, abnormal expression of some potential BCL2 antiapoptotic, the BCL-XL and XIAP can enhance the tumor cells to death signal resistance, in addition, caspase8 lacking expression can promote the invasion and metastasis of tumor cells.

1.2.3 Vascular extravasation overflow

Transfer cells the stagnated of capillary and spilled from the circulatory system are needed to reach the target tissue, this process is extravasation, because of the different tumors, the process have certain difference. In osteosarcoma, cytoskeleton anchor ezrin protein may promote the occurrence of the process.

1.3 The result of the transfer, the formation of colonization

Stephen Paget's seed-and-soil hypothesis prompt to spread of cancer cells or "seed" can only be implanted with the growth of compatible organ microenvironment, even if they are a large number of target on other organizations, and the success of metastases formation requires "seeds" and "soil" interactions.

1.3.1 Dormant cells

Dormant cells refers to an individual cell or micrometastases long-term survival, but no obvious further development. In some cases, if angiogenesis can not happen, they will make micrometastases outward growth restricted, at this time if angiogenic stimulation can effectively break the dormancy. Lewis lung cancer cells dormancy can be activated by angiogenesis or removal of the original site. In this case, the dormant represents the proliferation and apoptosis of tumor cells of a balance.

1.3.2 Organ specificity

Metastasis of tumor cells must interact with new environment effectively, survival, proliferation and generate new metastases, and different organs have different requirements for the growth of tumor cells.

1.3.3 Shifted again (seeding and reseeding)

The pulmonary metastasis of breast cancer is found, promotes to transfer all genes expressed in the original site, although these genes can promote the formation of metastases, but may be selectively expressed in the original site to provide growth advantage. These cells may form the ability of metastases in the primary site.

CONCLUSION

Tumor metastasis is a variety of cellular involved in complicated process, affected by many factors, including every link of failure leading to failure of the malignant transfer. Although tumor metastasis of each process has been further studied, but there are still many problems remain to be further research. Are transfer occurrence and the genetic heterogeneity random? Whether a cell is a single or cell mass transfer should be carried out. What is Intravasation and extrevasation concrete mechanism? Under normal circumstances, extracellular matrix protease, since the suppression (autoinhibition) and secretory tissue inhibiting conditions are strict controlled, such as how to transfer this strict regulation in the process of being broken. What's the difference between angiogenesis and normal

angiogenesis? What are the factors affecting organ specificity transfer decision? Will Abl kinase influence on transfer can inhibit or promote the universality? If PTPRO inhibits metastasis, in addition to the Abl, is there any other way? The answers can help us better understand the process of tumor metastasis and the clinical treatment of cancer.

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