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An insight into metastasis: Random or evolving paradigms?

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ABSTRACT

Mechanical or fostered molecular events define metastatic cascade. Three distinct sets of molecular events characterize metastasis, viz invasion of extracellular matrix; angiogenesis, vascular dissemination and anoikis resistance; tumor homing and relocation of tumor cells to selective organ. Invasion of extracellular matrix requires epithelial to mesenchymal transition through disrupted lamellopodia formation and contraction of actin cytoskeleton; aberration of Focal adhesion complex formation involving integrins and the extracellular matrix; degradation of extracellular matrix by matrix metalloproteases; faulty immune surveillance in tumor microenvironment and an upregulated proton efflux pump NHE1 in tumors. Vascular dissemination and anoikis resistance depend upon upregulation of integrins, phosphorylation of CDCP1, attenuated apoptotic pathways and upregulation of angiogenesis. Tumor homing depends on recruitment of mesenchymal stem cells, expression on chemokines and growth factors, upregulated stem cell renewal pathways. Despite of many potential challenges in curbing metastasis, future targeted therapies involving immunotherapy, stem cell engineered and oncolytic virus based therapy, pharmacological activation of circadian clock are held promising. To sum up, metastasis is a complex cascade of events and warrants detailed molecular understanding for development of therapeutic strategies.

1. Background

Metastasis, for long time was considered as a stochastic event, where accumulation of genetic or epigenetic alterations in different driver and passenger genes lead to dislodgement of the tumor cells from their primary site to distal organs [1]. However, data from different studies established that, although the genetic basis of tumorigenesis varies between different cancers, molecular events for metastasis are generally similar for all solid tumors.

A retrospective to the “mechanistic theory” of metastasis suggests a “seed and soil” theory highlighting the role of the anatomical location of the primary tumor and the number of live tumor cells in the capillary bed, as the determinants of metastasis [2]. Thus, it was seen that lung, renal, breast, melanoma, and colorectal cancers tend to metastasise in brain, whereas other cancers like prostate, ovarian, uterine, thyroid, liver, bladder, gastric, skin, and pancreatic neoplasms do not follow the same trend [3]. However, metastasis in reality is essentially complex phenomenon, without a concrete visual paradigm.

In a clinical setting, dealing with metastasis has always remained a major challenge for the clinicians, as the success rate of clinical trials is widely known to depend on parameters viz. the extent of metastasis, extent of differentiation of the cancer, few other pharmacological parameters play a major role on defining the success rate of clinical trials. Thus, to meet the therapeutic demand, identification of the candidate genes/pathways is incumbent.

Although a linear progression model cannot be drawn on these set of molecular events in metastasis, but a cumulative effect of them leads to dislodgement of tumor cells from their primary site and anchorage to another organ. While metastasis has been considered a global concern, previous studies were highly focussed on few well characterized molecular events like upregulation of integrins and junctional proteins, changes in tumor microenvironment or on apoptosis escape mechanism.In the present study, we have tried to define metastasis on the basis of hitherto best characterized stochastic, biochemical or idiopathic sets of events on the basis of their chronology.

2. Recent studies and results

Till today, a number of studies are being conducted to delineate the molecular mechanism of metastasis on a chronological order. Based on

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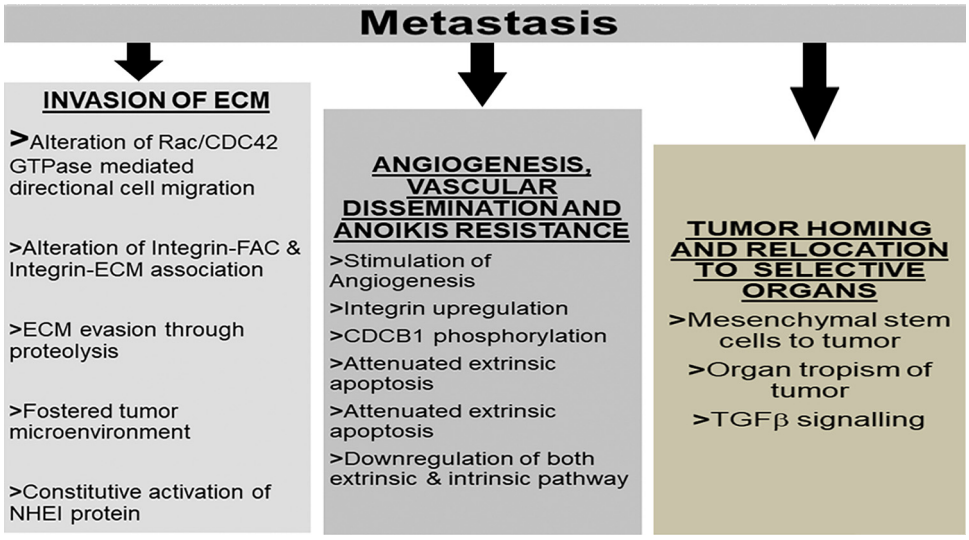

Fig. 1. Major molecular Events of metastatic cascade.

the available data, molecular mechanism of metastasis has been re-defined into three broad categories: [A] Invasion of extracellular matrix, [B] Stimulation of angiogenesis, vascular dissemination and anoikis resistance [C] Tumor homing and relocation of tumor cells to selective organ (Fig. 1).

2.1. Invasion of extracellular matrix

With increase in growth of tumors, pressure on the extracellular matrix builds up, leading to invasion of extracellular matrix by the tumor cells either collectively or individually [4]. Stromal cell derived chemokines drive the collective invasion, where, the leader cells of tumor mass express chemokine receptors; formpseudopodia like protrusion, make integrin mediated focal contact with the actin cytoskeleton and degrade the extracellular matrix. In collective amoeboid transition, β1 integrins are down-regulated [4]. For cell migration at individual cell level, the gain-in-potential for dislodgement from one another occurs through downregulation of E-Cadherin expression and/or mutation of Catenin genes and/or upregulation of mesenchymal cadherins viz. N-cadherin, integrin-αvβ6, vimentin, matrix metalloproteinase-9 [5,6]. Apart from a decrease in E-Cadherin expression and upregulation of protease activity, tumor cells individually gain invasive potential through an epithelial to mesenchymal transition, (EMT) wherein, upregulation in transcription factors, such as TWIST1, Snail, Slug, ZEB1/2 [4] as well as N-cadherin, vimentin, fibronectin and smooth muscle actin [7] induces a mesenchymal state in tumors with concomitant suppression of expression of epithelial markers [8], facilitating the extracellular matrix invasion. Earlier report suggested that highly metastatic clones of tumors express higher transcription of type IV collagenase to facilitate invasion; bFGF (basic Fibroblast Growth Factor) and IL-8 to facilitate angiogenesis [9]. A plethora of lytic enzymes like plasminogen activator, plasmin, cathepsin B, cathepsin D, glycosidases collagenases etc are also upregulated during tissue invasion [10].

In both collective and individual migration of tumor cells, cells acquire mesenchymal type of emigrational characteristics through aberrations of following pathways/cellular components viz. [a] Aberration of Rac/CDC42 GTPase and associated binding partner mediated lamellopodia formation and actin cytoskeleton contraction (Polarized cell migration),[b] focal adhesion involving of integrins β1 and β3 at the junction between the extracellular matrix and the cell, [c] activation of proteolytic enzymes (matrix metalloproteinases, serine and threonine proteases, cathepsins) at the “cell-matrix” interface resulting in the destruction and remodeling of the surrounding extracellular matrix, reorientation in the actin cytoskeleton polarization and finally dragging the cells of the trailing edge toward movement through the focal point, [d] Contact independent regulators in tumor microenvironment.

Candidate factors, contributing to acquisition of mesenchymal type characteristics by tumors are as follows:

2.1.1. Aberration of Rac/CDC42 GTPase and associated binding partner mediated lamellopodia formation and actin cytoskeleton contraction (Polarized cell migration)

From various other reports, it may be conferred that polarized migration leading to tumor metastasis is different from directional migration observed in normal cells, as, in tumors aberration of components regulating directional migration of cells are very frequent. APC, amajor gatekeeper protein, which, besides its role as mitotic regulator and negative regulation of stem cell renewal by canonical Wnt signalling pathway, is also known to regulate cell polarization, an important event for migration [11,12]. In normal cells, directional process of cell migration is also mediated by APC through a transient complex of APC-ASEF-IQGAP1-CDC42-GTP (Fig2A) [13], a process which is altered in cancer metastasis, presumably due to genetic or epigenetic alterations of APC in different types of cancer [11,14–16] (Fig. 2B). Loss of APC functionality is one contributing factor that could lead to impairment of recruitment of dephosphorylating complex on CDC42, leading to aberrant cell migration. In many cancers, overexpression of IQGAP1 recruits CDC42-GTP, leading to aberrant downstream signalling, leading to tumor invasion [17]. In this context, reduced expression of IQGAP2, a competitive binding partner of IQGAP1, with ability to bind CDC42, has also been observed in many cancers [18] (Fig. 2A, B).

2.1.2. Aberration of focal adhesion complex formation, involving of integrins β1 and β3 at the junction between the extracellular matrix and the cell

Physiologically, homeostasis in normal cells is maintained through tight cell–cell adhesion and cell–matrix adhesion, through interaction of cellular cytoskeleton like integrin with extracellular matrix molecules (ECM) like collagen, fibronectin, fibrinogen and laminin, through a group of transmembrane glycoproteins called Cellular Adhesion Molecules (CAM). The ECM-cytoskeleton interaction is maintained through focal adhesion complex, a complex group of kinases, scaffold and adaptor proteins that relay the proliferation signal from extracellular matrix to integrin and its associated downstream effector molecules like focal adhesion kinase (FAK), phosphatidylinositol 3-kinase (PI3K), extra-cellular signal-regulated kinase1and /mitogen activated