Cancer Treatment Reviews 40 (2014) 293–299

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Laboratory-Clinic Interface

The seed and soil hypothesis revisited: Current state of knowledge of inherited genes on prognosis in breast cancer ☆

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ARTICLE INFO

Article history:
Received 11 June 2013
Received in revised form 3 September 2013
Accepted 6 September 2013

Keywords:
Breast cancer
Metastasis
Gene expression
Tumor stroma
Polymorphism
Genetic background

ABSTRACT

The crucial event in the course of malignancies such as breast cancer is its metastatic spread from the primary tumor of origin to distant organs. The natural history of a tumor is determined by the expression of its genes, and in this sense, knowledge has advanced dramatically in recent decades. However, much less is known about the role that the patient plays in the behavior of a tumor. In this article, we review the evidence regarding the genetic background of the host in metastatic tumor dissemination, providing information from epidemiological studies as well as from animal models and human studies. Undoubtedly, the elucidation of possible interpersonal variability in susceptibility to developing metastases would significantly contribute to improve management of cancer patients.

Introduction

Up to 90% of cancer deaths are due to complications arising from metastatic dissemination of the disease [1]. Metastasis is an extraordinarily complex process, entailing tumor cells acquiring a set of features that allow them to develop new foci of the disease. Among such characteristics are rupturing of the basal membrane, loss of different intercellular junctions, migratory capacity from the primary tumor site or through the extracelluce, the mechanisms triggering the invlar matrix, incorporation into the blood or lymphatic stream and, ultimately, extravasation of tumor cells into the parenchyma of the secondary organ. Despite their importance, the mechanisms triggering the invasion metastasis cascade and the factors regulating these processes are not yet fully understood, and several different models have been proposed to explain the phenomena underlying tumor dissemination.

Models of metastatic growth

The most widely accepted theory is the progression or clonal selection model, proposed originally by Nowell [2]. According to this theory, only a small fraction of the tumor cells acquire the metastatic phenotype, through a series of somatic mutations as a late event in the course of the tumor. This theory is supported by Fidler's [3,4] experiments, in which B16 melanoma cells were injected into mice that developed pulmonary metastases. The metastatic capability of tumor cells sampled from the metastasis was seen to be greater than that of cells from the primary tumor. These results led to the suggestion that most of the primary tumor's cells had low metastatic potential. Therefore, they had acquired the metastatic phenotype during their development through additional somatic mutations. This model, based on cultured cell lines, has not been proved in other similar models in which the metastatic capacity of cells derived from metastatic foci was similar to that seen in the primary tumor cells [5,6]. Furthermore, the existence of cancer of unknown-primary site is against this theory. In these patients, the metastases are present at the onset of clinic disease without a primary tumor with enough larger size (i.e. number of cells) to achieve the required mutational events for the metastatic phenotype acquisition.

In an attempt to explain these observations that the dissemination capacity of the cells from secondary foci was not greater than that of the primary tumor cells, Weiss proposed another model called dynamic or compartmental heterogeneity [7]. Unlike the

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http://dx.doi.org/10.1016/j.ctrv.2013.09.010

clonal selection model, all the cells in a tumor would have the capacity to generate metastases, but due to epigenetic changes only a small portion of these cells would be able to complete the process of dissemination at a given moment in time. Some studies support Weiss theory, showing that methylation inhibitors are able to induce the development of metastatic phenotypes in mouse models [8,9]. However, given that methylation inhibitors can cause chromosomal impairments, the capacity to produce metastases after treatment with these agents may be due to mutational phenomena and not to real epigenetic changes [10].

Some of the capabilities that tumor cells must acquire to develop a distant focus are characteristics inherent to normal lymphoid cells such as proteolytic degradation or intra- and extravasation capabilities. Accordingly, the fusion model maintains that tumor epithelial cells would acquire such properties by incorporating DNA from lymphoid cells [11]. In physiological conditions, there are some examples of cellular fusion phenomena, like multinucleate skeletal muscle fibers derived from myocytes fusion. Moreover, some data from cell and animal models, as well as from human tumors, show that host and tumor cells do merge. Two cases of renal cell tumors have been reported in patients who received bone-marrow transplantations, containing both the patients' own and the marrow donors' DNA [12,13]. Also, in myeloma patients the presence of chromosomal translocations specific for myeloma has been identified in normal osteoclasts [14]. It is not clear, however, whether these findings play a role in the development of a metastatic phenotype or whether they are just a late event with no causal effect.

The metastasis gene transfer model provides a different approach. Here, metastases do not originate from circulating tumor cells, but instead from incorporating tumor DNA into circulating stem cells located in the target organ [15]. There are only experimental scant data to support this model of tumor dissemination, like murine tumors developed from normal fibroblasts in which H-ras (V12) and c-myc oncogenes have been taken up from apoptotic bodies [16].

Based on existing data about the role of stem cells in breast cancer tumorigenesis [17], some authors have maintained that only tumor stem cells are capable of initiating new metastatic foci. According to this model, if the malignant switch starts in stem cells, then tumors with poor prognosis and high metastatic capabilities will develop. However, if the transformation occurs in more highly evolved progenitor cells, then the neoplasm would have a more limited potential to generate distant foci [18]. These stem cells would be highly resistant to chemotherapy.

Many studies conducted since the 1990s using microarrays techniques have confirmed that tumors can be distinguished through their gene expression profiles, enabling us to determine whether primary tumors have the capacity to trigger metastases [19]. These data imply that the vast majority of tumor cells from the primary site have sufficient genetic information to develop metastases. Based on these findings, different groups have suggested that metastatic ability is an event occurring during the initial stages of oncogenesis and is conditioned by the same mutational events that may be involved in primary tumorigenesis [20]. Furthermore, Ramaswamy's group has also defined a set of 17 genes linked to metastatic phenotypes, regardless of the primary tumor origin [21]. The clonal dominance model is another interpretation of this theory, which states that the number of primary tumor cells with a metastatic phenotype progressively increases until they become the dominant population. Thus, most cells would be capable of initiating distant foci at a given moment in time [22].

All these models and theories share the common belief that it is mainly the tumor's characteristics that govern its capability for metastases. However, this is a complex biological phenomenon that involves both tumor cells (seed) and normal cells in the bloodstream and in the different target organs (soil). The findings by Massagué's group reveal the reality of this organ tropism, defined by Paget in the 19th century [23]. According to these results, there are different tumor cell subpopulations with different affinities to colonize certain target organs, depending on their genetic constitution. Tumor cells that overexpress the *CXCR4, PTHLH, IL11, MMP1* and *OPN* genes have the ability to promote bone metastases [24], while cells that overexpress *COX, EREG* and *ANGPTL4* exhibit a tropism for the lung [25]. In addition, tumor cells overexpressing *ST6GALNAC5, COX2, HBEGF* and *ANGPTL4* have a particular affinity for colonizing the central nervous system [26]. Presumably, the gene patterns specific to each of these cell subpopulations may be obtained through a series of somatic changes [27].

Cells from host's immune system also play a key role in modulating the tumor microenvironment. Several innate and adaptative immune cell types, effector molecules and pathways can sometimes function as extrinsic tumor-suppressor mechanisms [28]. However, tumors develop even in presence of an intact immune system and become eventually clinically detectable. That occurs because the immune system plays a dual role in cancer: it not only suppresses tumor growth but also promotes tumor progression by selecting more aggressive tumor variants to survive in an immunocompetent host or by modulating the tumor microenvironment in order to facilitate tumor outgrowth [29]. Thus, the differences in an individual's immune repertoire, the antigens processing and presenting capacity, the generation of tumor antigens and the ability of cancer to suppress immune response will determine the overall outcome of a particular tumor in an individual [30].

Genetic predisposition model

Over the last decade, many published papers have stressed the importance of cells from tumor stroma, both in primary tumorigenesis and in the process of metastasis. The contributions made by different host-cell types, that comprise the tumor microenvironment, are integrated within a system of heterotypic signalling interactions that enable the acquired capacity for invasive growth and metastatic dissemination [28]. These data provide a broader view of the influence of these host characteristics on the course and behavior of the neoplasm. According to the premises of the genetic predisposition model, the patient's germline genetic burden would also be involved in the expression of the metastatic phenotype of a tumor, just as constitutional polymorphisms are responsible for expressing other features or characteristics of the individual.

Animal studies

Hunter's group showed in mouse models that the metastatic behavior of a tumor induced by the same oncogenic event, the antigen of the polyoma T virus, differed according to the germline genetic burden for each of the strains used (Fig. 1). The FVB/NJ mouse strain constitutionally expressed the oncogene of the polyoma T virus, which induced the development of highly aggressive, multiple and synchronous breast tumors in almost all virgin females, with over 85% of the animals developing pulmonary metastases at 100 days of life [31]. In successive experiments by this group, male FVB/NJ mice were mated with different homozygotic strains of female mice, and the density of lung metastases was studied in the F1 progeny. The authors found that there was significant variation in the density of lung metastases according to the female mouse strain used. For instance, and taking the pulmonary density present in the F1 progeny from the FVB/NJ strain as a reference, the density of metastases in the progeny of the DBA/2J