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Review

Genetics and metabolic deregulation following cancer initiation: A world to explore

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ABSTRACT

Cancer is a group of highly complex and heterogeneous diseases with several causes. According to the stochastic model, cancer initiates from mutation in somatic cells, leading to genomic instability and cell transformation. This canonical pathway of carcinogenesis is related to the discovery of important mechanisms that regulate cancer initiation. However, there are few studies describing genetic and metabolic alterations that deregulate transformed cells, resulting in epithelial–mesenchymal transition (EMT) and its most dramatic consequence, the metastasis. This review summarizes the main genetics and metabolic changes induced by reactive oxygen species (ROS) that lead to EMT.

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1. Hypothetical models for carcinogenesis

Cancer is a group of highly complex and heterogeneous diseases [1] with multifactorial causes [2]. Studies that aim to elucidate the oncogenic process have been proposed for centuries [3,4]. However, in last decades, the stochastic model became a paradigm to describe carcinogenesis [1,2,5].

Stochastic model was first proposed by the surgeon and oncologist Karl-Heinrich Bauer in 1928 [1]. This model was widely accepted, especially after the DNA structure description in 1953. According to this model, somatic cells accumulate mutations, which can fixate, resulting in genomic instability and cell cycle deregulation [5,6]. These actions can lead to cell transformation, characterized by the acquisition of inheritable properties, such

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as: growth potential, morphological and energetic metabolism changes [4,7,8]. Thus, transformation could be evidenced in weeks, while carcinogenesis, in months or years [7]. Thus cancer is the result of slow and gradual process of genetic and morphological changes [9].

In the last decades, new models were proposed to improve the understanding of these processes, discussing the carcinogenesis [1]. These models are based on tumor microenvironment understanding [10,11]. According to these models, cancer emerges from: (1) a pathogenic stimulus, induced by physical, chemical or biological agent and (2) a chronic and subclinical inflammation accompanied by (3) fibrotic process [1]. Together, these changes increase the reactive oxygen species (ROS) production [12], leading to loss of tissue homeostasis, contributing to cancer development [1,4]. Thus, oncogenic process comprises different steps: (1) mutation or genomic instability (cancer initiation), (2) cell transformation, (3) promotion, (4) progression and (5) metastasis [1,4]. However, cancer initiation remains dependent on DNA damages (mutations), which are mandatory to promote genomic instability, reinforcing stochastic model [1]. For this reason, mutagen identification has been explored [13–16], since to avoid the long term exposure to these mutagens can be considered a protective method against cancer. Currently, it is known that several drugs [16–18], organic [19–22] and inorganic chemical compounds [23,24] and biological agents, including viruses [12,25–33] are able to induce DNA damage.

Although cancer initiation is strictly dependent on mutations, promotion and progression depend on different coordinated events, which result in tissue homeostasis loss [34]. These events are characterized by genetic and metabolic deregulations, that lead to extracellular matrix (ECM) degradation and acquisition of migratory phenotype in epithelial cancer cells [35–37]. These actions characterize a pathological process known as epithelial–mesenchymal transition (EMT), responsible for invasion and migration of cancer cells for distant organs (metastasis) [34,38,39]. For these reason, genetic and biochemical alterations in cell adhesion-associated components, such as immunoglobulin, integrins, cadherins, selectins are verified during EMT [1]. However, these alterations verified after cancer initiation remains few explored, especially in relation to oncogenic viruses-associated malignances. Thus, this review focus on genetic and metabolic deregulations verified in tumor microenvironment after cancer initiation, resulting in the most dramatically consequence of the disease, metastasis.

2. Epithelial–mesenchymal transition (EMT)

In last decades, novel diagnostic methods and therapies have been implemented related to cancer [40]. However, despite these advances, the number of patients that succumb has increased globally [40]. One of the reasons is the chemotherapeutic resistance developed by cancer cells [4,40]. This resistance emerges as a consequence of cell plasticity and heterogeneity in relation to cell types that compose tumor microenvironment [40,41].

Epithelial cell plasticity is a metazoan conserved characteristic [11]. Epithelial cells are characterized by apical-basal polarity and a strong intercellular adhesion [42,43]. This adhesion is conferred by calcium-dependent adherent junctions, desmosomes connected to intermediate filaments of cytoskeleton and the interaction between epithelial cells and ECM [43]. Thus, epithelium constitutes a physical barrier [44], which integrity is crucial for tissue homeostasis [45].

Mesenchymal cells, in general, do not present intercellular contact, neither apical-basal polarity [43,44]. These cells are morphologically irregular and fusiform [44]. They express metalloproteinases (MMPs) able to remodel the ECM [43] and signaling proteins that act on epithelial cells, such as growth factors: epidermal (EGF), fibroblastic (FGF) and transforming β (TGFβ) [43]. Overexpression of these factors in solid tumors are associated to worse prognosis [42].

In this context, EMT emerges as a biological reprograming process, characterized for a series of coordinated events in which epithelial cells obtain a mesenchymal phenotype (transdifferentiation), conferring migratory and invasiveness ability associated to anoikis resistance (ability to evade the programmed cell death dependent of adhesion loss) (Fig. 1) [46–50]. For this reason, cells in EMT are resistant to chemotherapies and adjuvant drugs employed in cancer treatment [41,51].

Transdifferentiation of epithelial to mesenchymal cell was first reported in 1908 by Frank Lillie and, later described by Elizabeth Hay in corneal epithelial tridimensional (3D) cell cultures [35,52,53]. EMT is crucial along the embryogenesis [44,51,54]. During gastrulation, EMT gives rise to mesoderm, responsible for muscle, bone and connective tissues formation [55]. In neural crest delamination, this process is responsible for glial cells, adrenal gland and epithelial pigmented cell formation [55]. In adults, EMT is responsible for morphogenesis and tissue regeneration [55]. However, unappropriated activation of EMT during adult life causes important disturbs on epithelial tissue homeostasis and integrity, which are associated to several diseases, including cancer [47]. So, there are three types of EMT: (1) type 1—observed during embryogenesis, (2) type 2—observed during tissue regeneration or healing associated to fibrosis and (3) type 3—associated to carcinogenesis, cell migration, invasion and metastasis [50,56], present in both carcinomas and sarcomas [35]. This review emphasizes some of mechanisms that control EMT type 3.

3. EMT hallmarks

EMT can occur in any epithelial cell [44]. One example of this transdifferentiation is the endothelial-mesenchymal transition (EndoTM), in which vascular endothelial cells can originate myofibroblast [44]. However, EMT is verified in tumor-stroma interface (invasion front) [39]. This process is regulated by different biochemical, genetic and morphological changes, which promote cell adhesion loss and acquisition of migratory phenotype [37,41–43,57]. Thus, EMT confers the cell polarity loss, resulting in asymmetric cell division [45].

Asymmetric cell division is responsible for the maintenance of heterogeneity of cell types in epithelium, being observed during stem-cell division [4]. Asymmetric division originates two daughter cells: one differentiated and other, undifferentiated (stem-cell like) [55]. Thus, asymmetric division of cancer stem-cell (CSC) results in one differentiated cancer cell and one CSC [1,45,47]. Continuous division of these cells is responsible to keep a CSC population in the tumor microenvironment. A clinical example of the process is observed in breast cancer, where asymmetric division of epithelial cells that express mesenchymal morphology ($CD44^{+}/CD24^{low}$) is responsible for the maintenance of CSC, which confers to them therapeutic resistance [55,58–60]. Thus, loss of polarity is considered a EMT hallmark [45].

Loss of cell polarity is a directly consequence of genetic cadherin switching. This process is characterized by genetic repression of epithelial cadherin (E-cadherin) promoter, followed by the neural cadherin (N-cadherin) gene expression, reducing the intercellular adhesion [11,35,44,61]. For these reasons, the E- to N-cadherin genetic switching is another important EMT hallmark, being observed in the first steps of carcinogenesis [35,42,45,47,49,62].

E-cadherin is a transmembrane glycoprotein [42], constitutively expressed, that mediates calcium-dependent homophifilic