Improved Version of Cancer Evo-Dev, a Novel Scientific Hypothesis Derived From Advances in Hepatitis B Virus (HBV)-Induced Hepatocarcinogenesis

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Abstract

A novel scientific hypothesis Cancer Evo-Dev is presented based on hepatitis B virus (HBV)-induced carcinogenesis. The framework of improved version covers following aspects. Interaction of genetic predispositions and environmental insults contribute to non-resolving inflammation. Inflammatory factors promote somatic mutations in the viral or human genomes via inducing imbalance between the mutagenic force and mutation-repairing force. The inflammatory microenvironment selects mutated viruses and the virus-altered host cells, and also drives retro-differentiation of the mutated host cells into cancer stem-like cells. Cancer stem-like cells preferentially utilize glycolysis for energy production to survive and also for generating the raw material to proliferate themselves in the hostile microenvironment. Key molecules involved in this evolutionary-developmental process of Cancer Evo-Dev can be applied for the prediction, prophylaxis, and targeted treatment of malignant diseases.

Introduction

Chronic but active inflammation, which is activated and maintained by stimulants such as infection and the interactions of stimulants with genetic predisposition, facilitates the occurrence and recurrence of cancers of various histotypes. Chronic inflammation, apparent or unapparent, is indispensible for the development of most malignancies, which has been clarified in hepatitis B virus (HBV)-induced hepatocellular carcinoma (HCC). Based on our previous work and the advances of researches on HBV-induced HCC and other inflammation-associated cancers, we presented the framework of a novel cancer theory termed Cancer Evolution and Development (Cancer Evo-Dev) [1-3]. Actually, Cancer Evo-Dev can be applied in cancers of many histotypes.

The major components of this theory are listed as follows.

I. Interaction of genetic predispositions of key immune- or inflammatory molecules and environmental insults including chronic HBV infection contributes to imbalance of immunity that is essential to arouse and maintain inflammation. We have found that the genetic polymorphisms of signal transducers and activators of transcription 3 (STAT3), nuclear factor-κB (NF-κB), HLA-DP, and HLA-DQ are significantly associated with the generation of the end-stage liver diseases-associated HBV mutations, the persistence of HBV infection, and increased risks of developing liver cirrhosis and HCC in chronic HBV-infected subjects [4-7].
APOBEC3s not only promote somatic mutation and viral mutation but also alter epigenetic modification of some genes by deaminating 5-methylcytosine or 5-hydroxymethylcytosine directly in concert with base-excision repair to exchange cytosine, thus promoting gene demethylation and removing epigenetic memory to stabilize the pluripotent state in embryonic stem cells. By this way, AID/APOBEC3s promote epithelial-to-mesenchymal transition (EMT), a process that is critical in embryonic development and cancer metastasis [12]. Thus, AID/APOBEC3s bridge non-resolving inflammation and the occurrence and recurrence of cancers.

III. Most of the mutated cells and viruses are cleaned up in the hostile microenvironment. Only a small proportion of the mutated cells whose somatic mutations change their survival signalling adapt to the hostile microenvironment, retro-differentiate via promoting EMT by AID/APOBEC3s, and reversely develop into the so-called tumor-initiating cells or cancer stem cells. During the development from the embryo to adult, most genes expressed at the embryonic stage are going to be silenced after birth. Some fetal proteins such as α-fetoprotein (AFP) or carcinoembryonic antigen (CEA) can re-express temporarily if some tissues like liver or testis quickly are injured and repaired. Interestingly, when some cancers develop, these fetal proteins can re-express persistently and serve as the biomarkers of cancers in the circulations of patients. Thus, carcinogenesis represents a reverse-developmental process, namely, transformation from differentiated cells into undifferentiated cells. The oncotel protein AFP and CEA serve as diagnostic biomarkers of HCC and other gastrointestinal malignancies, respectively. Another oncotel protein, SALL4, is a transcriptional factor that regulates developmental events, embryonic stem cell properties, and cancers. The expression of SALL4 is high in human fetal liver and silenced in the adult liver, but it has been proven to be re-expressed in some HCC. The re-expression of SALL4 in HCC subsets represents the "stemness" that confers the invasion and unfavourable prognosis [13]. Embryonic or stem-like gene signatures expressed in the tumors of diverse histotypes are robustly related to EMT and increased self-renewal and aggressiveness of cancer cells as well as poor postoperative prognosis [14]. During cancer invasion via EMT, epithelial cancer cells acquire "stemness," including self-renewal and anti-apoptotic capacities. Within the tumor masses, only a small proportion of tumor cells with the "stemness" feature become the major malignant cell subpopulations in the different branches of primary and metastatic masses, thus forming tumor heterogeneity. These tumor subpopulations should be cancer stem cells of distinct potentials, contributing to the metastatic nature and chemo-resistance. Thus, retro-differentiation and reverse-development are the major characteristics of cancer development.

IV. Under the cultivation of tumor-promoting factors such as POSTN from tumor-infiltrating neutrophils, tumor-infiltrating fibroblasts, and tumor-infiltrating macrophages (M2 type), tumor-initiating cells acquire the "stemness". Cancer-stem cells survive under the selection procedure from distinct microenvironments and acquire capabilities of distant metastasis and drug-resistance [15].

V. Cancer cells preferentially utilize glycolysis for energy production, even in the presence of oxygen, to support rapid growth of cancer cells, a phenomenon known as the Warburg effect. The Warburg effect in M2 macrophages promotes the formation of vascular network, augments extravasation of tumour cells, and induces a higher level of EMT within the tumors [16]. The Warburg effect provides not only essential energy for cell survival but also the raw material for DNA synthesis in the fast proliferating cells.

Thus, the development of malignant disease is characterized by an evolutionary process of "mutation-selection-adaptation". The framework of improved Cancer Evo-Dev can be verified in other cancers such as cancers of the breast, cervix, head & neck, colon & rectum, ovary, stomach, biliary tract and lung & bronchi [9,17]. Key molecules involved in the critical steps of the evolutionary-developmental process can be applied for the prediction of occurrence and postoperative recurrence as well as specific prophylaxis of malignant diseases. In addition, the key molecules in the functional signalling pathways that contribute to the stemness and promote cancer evolutionary-developmental process can serve as specific therapeutic targets for the inhibitors, thus providing a specific therapeutic strategy for a given advanced malignant disease. Thus, Cancer Evo-Dev has the following major functions in cancer prevention and control. The first, it can be applied to identify which precancerous lesion is more likely to develop cancers and to reduce the occurrence of cancers via removing or treating the dangerous precancerous lesions. The second, it can be applied to test what kinds of prophylactic and/or therapeutic options can reduce the incidence of malignancy and delay the postoperative occurrence. The third, it helps in developing individualized targeted therapy to block the key signalling pathways specifically and terminate the evolution and development of malignancies.

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