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Review

Curbing tumorigenesis and malignant progression through the pharmacological control of the wound healing process

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ABSTRACT

The prevention of cancer development and its progression is an urgent unmet medical need. Novel knowledge on the biology of cancer has evidenced that genetic changes occurring within cancer cells contribute, but are not sufficient, for tumor promotion and progression. The results of clinical studies and experimental animal models have suggested pursuing new avenues for the prevention of cancer development in the early stages, by using drugs that modulate platelet responses and those interfering with the synthesis and action of the mediators of inflammation. In fact, malignant tumors often develop at sites of chronic injury associated with platelet activation and chronic inflammation. In this review, we cover the evidence supporting this hypothesis and the rationale for the pharmacological treatment with antiplatelet agents, including low-dose aspirin, and antiinflammatory drugs to curb tumorigenesis and malignant progression. The evidence for a chemopreventive effect of low-dose aspirin against colorectal cancer (CRC) has been recently found appropriate by the U.S. Preventive Services Task Force, which recommends the use of the drug for primary prevention of cardiovascular disease and CRC.

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1. Introduction

Despite intense effort by scientific research to clarify the biology of cancer and to develop novel treatments, a gradual increase in the lifetime risk of developing cancer has been reported [1]. It has to be recognized that, when cancer has already developed, the improvement in care currently only prolongs survival: more efficacious and safer therapeutic strategies are needed [2]. To achieve these objectives, it is necessary to improve our current knowledge about the hallmarks of cancer; moreover, it is important to clarify mechanisms concurring in the early phases of tumorigenesis together with those orchestrating the malignant progression to a metastatic disease.

In the present review we focus on experimental and clinical evidence that indicate the role of abnormal wound-healing in the development of cancer. Moreover, we will discuss new possible pharmacological approaches to counter the development of cancer at early stages and to elicit the invasion-metastasis cascade.

2. The role of stroma in tumorigenesis

The hallmarks of cancer comprise several biological capabilities acquired during its multistep development: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming of energy metabolism, and evading immune destruction [2]. It is now clear that genetic changes occurring in cancer cells contribute, but are not sufficient, for tumor promotion and progression. All tumors have a stroma that is required for their nutritional support and the removal of metabolism byproducts [3]. A tumor is largely a product of the host, and is induced as the result of tumor cell-host interactions. In solid tumors, the stroma includes connective tissue, blood vessels, inflammatory cells and fibroblasts (Fig. 1). However, the stroma of solid tumors may also limit the influx of inflammatory cells or may impose a barrier to limit the escape of tumor cells and their invasion of distant normal tissues. Thus, during tumor progression, the phenotypic characteristics of the stromal cell types, as well as of the

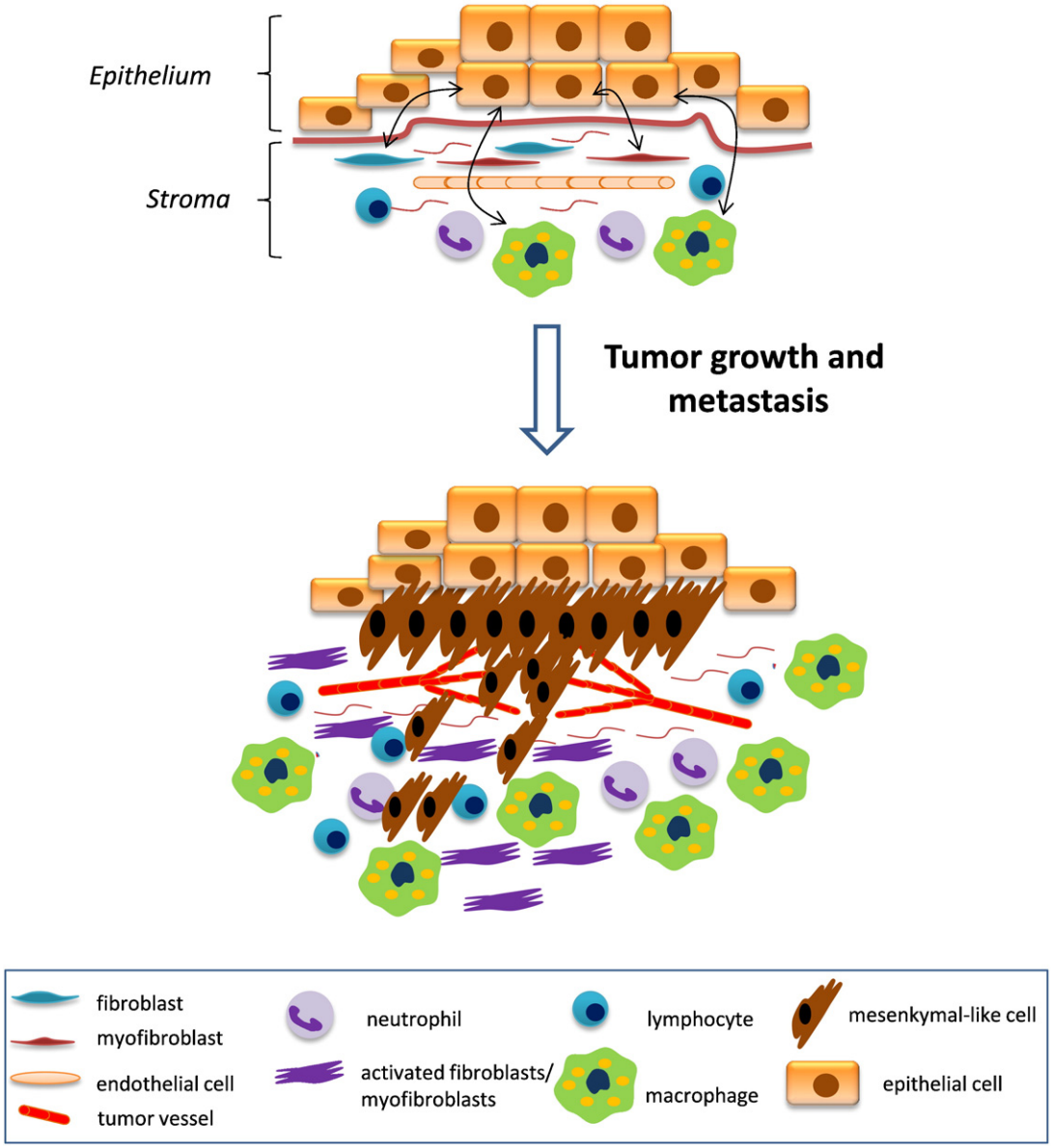

Fig. 1. Changes in stromal cell composition and functions during tumorigenesis. In the early phase of the development of solid tumors, the activation of stromal cells induces the release of several mediators, which contribute to the development of a persistent inflammation, typical of an unabated form of wound healing. In this scenario, epithelial cells acquire different cellular capabilities, including excessive proliferation sustained by enhanced angiogenesis and inhibition of apoptosis. Moreover, some cells change their phenotype, with loss of epithelial and a gain of mesenchymal cellular characteristics that enhance migration and invasion.

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