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Antihistamines as promising drugs in cancer therapy

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ABSTRACT

Histamine is a biogenic amine, synthetized and released by mast cells, which acts as a vasodilator in several pathologic processes, namely in allergies and conjunctivitis. Its role on cancer is not fully understood. High levels of histamine have been associated with a bivalent behavior in regulation of several tumors (*i.e.* cervical, ovarian, vaginal, uterine, vulvar, colorectal cancer, and melanoma), promoting or inhibiting their growth. Histamine receptors (H1, H2, H3 and H4) are present in a vast group of cells, including tumor cells, making them sensitive to histamine variations. In this work, we review the role of mast cells and histamine on cancer development and the possibility of use antihistamines in the clinical management of this disease.

Contents

1. Cancer

Cancer is one of the most important public health problems in many countries around the world. Despite all advances in the diagnosis and treatment of this disease, it is still one of the principal causes of death

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globally [1]. According to the World Health Organization (WHO) [2], approximately 14 million new cases and 8.2 million deaths from cancer were recorded in 2012. Moreover, disappointing projections are being pointed for the next years, with an increase in the number of new cancer cases *per* year to 22 million over the next two decades [3]. Cancer is a multistage process that arises from genetic and epigenetic alterations responsible for the transformation of normal cells into neoplastic cells [4–6] (Fig. 1). Cancers are not only masses of malignant cells but complex "rogue" organs, to which many other cells are recruited and may be changed by the transformed cells. The interactions between the malignant and non-transformed cells constitute the tumor microenvironment [7]. Lymphatic and vascular endothelial cells, pericytes, adipocytes, mesenchymal stem cells, smooth muscle cells, fibroblasts, myofibroblasts, myeloid cells and inflammatory cells (B and T lymphocytes, neutrophils, dendritic cells, eosinophils, basophils, natural killer cells, macrophages and mast cells) are among the non-malignant cells of tumor microenvironment [6,8]. These cells may be identified in the tumor microenvironment by their specific cell surface molecules and may act as tumor-promoting at all stages of carcinogenesis [9]. Each of them have the capacity to synthesize cytokines, reactive oxygen species (ROS), serine and cysteine proteases, metalloproteinases, growth and pro-angiogenic factors, inflammatory and matrix remodeling enzymes, chemokines, and adhesion molecules that interact among them and with tumor cells promoting tumor growth, invasion and dissemination to other organs (metastization) [10–13]. The evolution, structure and activities of cells in tumor microenvironment have many parallels with the processes of wound healing and inflammation; however, cells such as macrophages may be found in cancers that have no known association with chronic inflammatory conditions [14–16]. Now, it is known that targeting the non-malignant cells of tumor microenvironment or mediators of communication among them could complement other cancer therapeutic approaches, such as chemotherapy and radiotherapy. However, questions about the similarity of tumor microenvironment among different types of cancer, and between primary cancers and metastasis remain unclear.

2. Mast cells

Mast cells are bone-marrow derived leukocytes that were first described by Paul Ehrlich more than 130 years ago in his PhD thesis [17]. Mast cells were identified in all vertebrates [18] and some authors consider that they may be primitive cells, maybe the surviving remnant of an ancient model of the immune system [19]. Actually, mast cells are strategically placed at the host/environment interfaces. They may be found in proximity to surfaces that are common portals of infection, namely in mucosa of the respiratory, digestive and urogenital tracts, and in the dermis of the skin. Mast cells may also be found in the connective tissue near vessels and nerves, making them key elements in processes of tissue remodeling, wound healing, fibrosis and angiogenesis, and in the central nervous system where the histamine acts as a neurotransmitter [20,21]. Mast cells are not found in avascular tissues, namely mineralized bone, cartilage and cornea [22]. At histological analysis, mast cells appear as round or elongated cells with a diameter ranging from 8 to 20 μm. They have a non-segmented monolobed nucleus

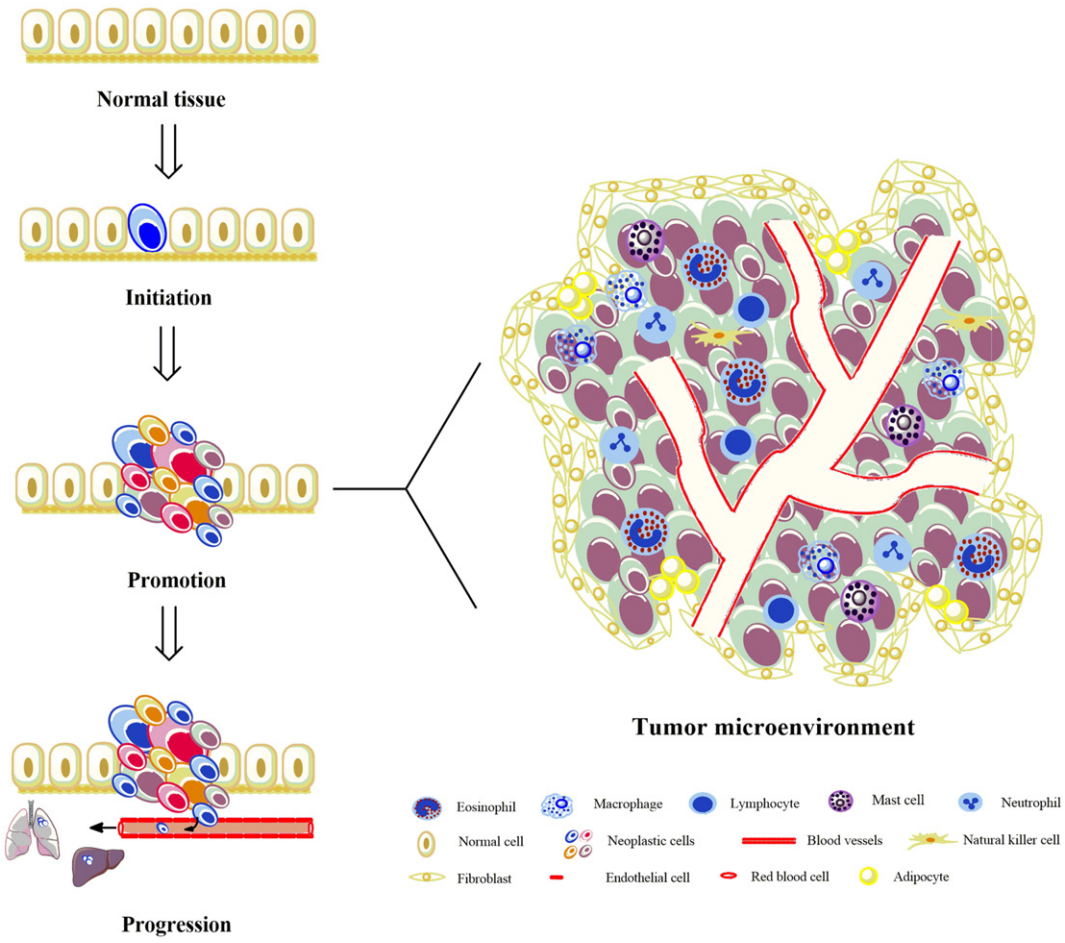

Fig. 1. Schematic representation of carcinogenesis stages and tumor microenvironment. Cancer begins with the mutation of one cell (Initiation), then this cell divides itself originating other mutated cells (Promotion). During this process, tumor is reached by several inflammatory and non-inflammatory cells that constitute tumor microenvironment. As last step, tumor cells go to other tissues, originating a new tumor in distant organs (Progression).