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Mast cells in lymphomas

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ABSTRACT

Tumor microenvironment is involved in the pathogenesis and progression of human lymphomas. The lymphoma microenvironment is composed by stromal cells, immune cells (macrophages, plasma cells, mast cells, eosinophils, basophils, T- and B-cells), blood vessels and extracellular matrix proteins. This article is focused on the role of mast cells in lymphoma progression and angiogenesis. Mast cells might be regarded in a future perspective as a new target for the adjuvant treatment of tumors, including lymphomas.

1. Introduction

Lymphomas constitute a large group of more than 40 lymphoproliferative disorders, classified on the basis of morphological, immunological, genetic, and clinical criteria. They typically arise in lymphoid tissues, even if extra-nodal localizations, in any organ of the body, are not uncommon.

In 1994, a revised European-American classification of lymphoid tumors (The REAL classification) was proposed by the International Lymphoma Study Group (Table 1) (Harris et al., 1994). This group distinguished three major categories of lymphoid malignancies, which included B-cell, T-cells and Hodgkin's lymphoma (HL).

Non Hodgkin lymphomas (NHL) are a heterogeneous group of lymphoproliferative malignancies with different patterns of behavior responses to treatment. B-cell lymphomas represent approximately 88%, and T- and NK-cell lymphomas 12% respectively, of all NHL. Among B-cell lymphomas, the incidence of diffuse large B-cell lymphomas (DLBCL) is 30%, of follicular lymphoma (FL) 25%, of extra-nodal marginal zone lymphoma of mucosa-associated lymphatic tissue (MALT lymphoma) 7%, of chronic lymphocytic leukemia 7%, of mantle cell lymphoma 5%.

The neoplastic cell of classical HL is the Reed-Sternberg cell, a large cell with two or more nuclei or nuclear lobes, each of which contains a large eosinophilic nucleolus, first described more than 100 years ago (Fig. 1). For correct diagnosis of HL, Reed-Sternberg cells must be found in an appropriate background consisting of a variable polymorphous reactive infiltrate of inflammatory and accessory cells (Harris, 1999).

Lymphoid tumors are generally divided into one of two categories, namely indolent lymphomas versus aggressive lymphomas, based upon on the characteristics of the disease at the time of presentation and the patients' life expectancy if the disease is left untreated. Generally, T cell lymphomas have a more aggressive clinical behavior than B-cell lymphomas of comparable histology and patients with mantle cell lymphomas or anaplastic large lymphomas have a 5-year survival rate of approximately 30% and 80%, respectively (Fisher et al., 1998).

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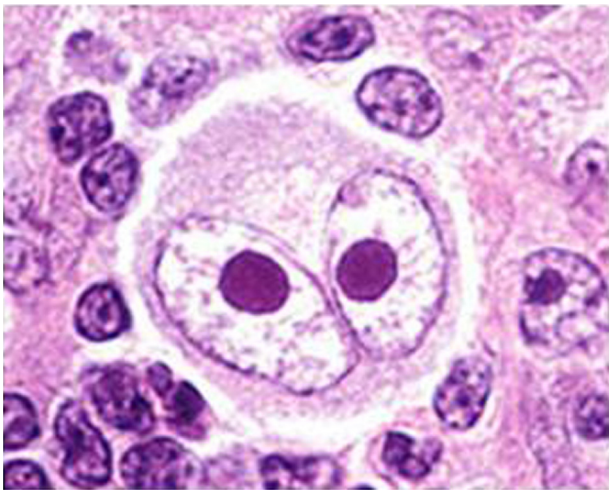

Fig. 1. A classical Reed-Sternberg cell. Reproduced from www.hematopathology.stanford.edu.

Fig. 2. Tryptase ia angiogenic in vivo in the CAM assay. Macroscopic pictures of CAM at day 12 of incubation, treated with tryptase. Note the presence of numerous blood vessels converging toward the implant. Modified from Ribatti et al. (2011).

It is well documented that neoplastic cells are influenced by their microenvironment and vice-versa. The specific organ microenvironment determines the extent of cancer cell proliferation, angiogenesis, invasion, and survival. This indicates that a permissive stromal environment is important in supporting tumor progression in combination with genetic alterations. Tumor cells are surrounded by an infiltrate of inflammatory cells, namely lymphocytes, neutrophils, macrophages, and mast cells, which communicate via a complex network of intercellular signaling pathways, mediated by surface adhesion molecules, cytokines and their receptors.

More recently tumor microenvironment has been involved in the pathogenesis and progression of human lymphomas. The lymphoma microenvironment is composed by stromal cells, immune cells (macrophages, plasma cells, mast cells, eosinophils, basophils, T- and B-cells), blood vessels and extracellular matrix proteins.

2. Role of mast cells in tumor growth and angiogenesis

Since the first recognition by Ehrlich in 1878, mast cells have often been observed at different sites of neoplasms. Mast cells are commonly recognized at the margins of diverse tumors in human and rodents, and are prominent in the tumor microenvironment, are thought to provide a host response of the innate immunity to neoplasia and could either promote or inhibit tumor growth depending on the local stromal conditions.

Mast cells play a role in tumor growth and tumor-related angiogenesis, by releasing in the tumor stroma cytokines and growth factors, which have detrimental effects to the host by stimulating tumor cell expansion. Mast cells are a major source of histamine, which can induce tumor cell proliferation through H1 receptors, while suppressing the immune system through H2 receptors (Ribatti and Crivellato, 2011).

In addition, mast cells synthesize and store angiogenic factors as well as matrix metalloproteinases (MMPs), which promote tumor vascularization and tumor invasiveness, respectively. In particular, mast cells are also involved in the production of pro-angiogenic factors, including fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β) and nerve growth factor (NGF) (Ribatti and Crivellato, 2011).

Moreover, tryptase contained in mast cell secretory granules, stimulate the proliferation of endothelial cells, promote vascular tube formation in vitro, angiogenesis in vivo in the chick embryo chorioallantoic membrane (CAM) assay (Fig. 2) and the release of VEGF or FGF-2 from their matrix-bound state through activation of MMPs and plasminogen activator (Blair et al., 1997; Ribatti et al., 2011).

Mast cells may generate immunosuppression by releasing IL-10, histamine and TNF-α, inhibit tumor cell growth, apoptosis and inflammation by releasing IL-1, IL-4, IL-6, and TNF-α. Finally, chondroitin sulphate may inhibit tumor cell diffusion and tryptase causes both tumor cell disruption and inflammation through activation of protease-activated receptors (PAR-1 and -2) (Ribatti and Crivellato, 2011).

3. Mast cells in lymphomas

The importance of angiogenesis in lymphoproliferative disorders has been studied in relation to their impact on the prognosis of patients, suggesting high relevance in different types of lymphomas (Kini, 2004; Koster and Raemaekers, 2005; Marinaccio et al., 2014a; Ruan et al., 2009).

An increase in tumor angiogenesis was reported in canine lymph node lymphoma compared to normal canine lymph nodes (Ranieri et al., 2005; Wolfesberger et al., 2008), and tumor growth of human cutaneous lymphoma model was significantly decreased in mast cell-deficient mice (Rabenhorst et al., 2012).

In classical HL high number of intratumoral mast cells is associated with nodular sclerosis subtype histology (Molin et al., 2002) and with poor prognosis (Keresztes et al., 2007). Otherwise, a lower number of mast cells is recognizable in Epstein Barr virus (EBV)-positive tumors, compared to EBV-negative tumors (Glimelius et al., 2011). Mast cells stimulate Hodgkin Reed-Sternberg (HRS) cell lines in vitro via CD30 ligand-CD30 interaction (Molin et al., 2001). Severe Combined Immunodeficiency (SCID) mice inoculated with HRS cells and mast cells developed significantly larger tumors with an increased vascularization, as compared with mice inoculated with HRS cells alone (Mizuno et al., 2012).

A striking association between tryptase-positive mast cells and microvessel counts has been found in benign lymphoadenopathies and B-NHL, and both parameters increase in function of tumor progression accordingly with Working Formulation malignancy grades (Ribatti et al., 1998, 2000).

Fukushima et al. (2006, 2001) assessed in NHL the cellular expression of VEGF and FGF-2, as well as mast cell and vessel counts.