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Mini-review

Microenvironmental interactions in classical Hodgkin lymphoma and their role in promoting tumor growth, immune escape and drug resistance

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ABSTRACT

Classical Hodgkin lymphoma (cHL) is characterized by few tumor cells surrounded by immune cells, fibroblasts, specialized mesenchymal stromal cells and endothelial cells, representing together with their products an active part of the disease.

Hodgkin and Reed–Sternberg (HRS) cells can secrete cytokines/chemokines and angiogenic factors capable of recruiting and/or inducing the proliferation of the surrounding cells and can also interact with distant sites of the microenvironment by secreting exosomes. To escape from a useful anti-tumor response due to the recognition by T and NK cells, HRS cells down-regulate HLA molecules, produce immune suppressive cytokines that inhibit cytotoxic responses, and induce an immunosuppressive phenotype on T lymphocytes and Monocytes. HRS cells survive, proliferate and are protected from the cytotoxic effects of chemotherapy agents by soluble factors or by the direct contact with inflammatory and stromal cells of the tumor microenvironment (TME).

A summary of the current knowledge about classical Hodgkin Lymphoma focusing on the cross-talk between tumor cells and the microenvironment leading to immune-escape, angiogenesis tumor growth/survival and drug resistance will be reviewed here.

General background

Hodgkin Lymphoma (HL) first involves lymph nodes [1]. It is characterized by a minority of tumor cells (less than 1% of the total cell population), collectively termed Hodgkin and Reed–Sternberg (HRS) cells, representing the small, mono-nucleated Hodgkin (H) cells and the large, binucleated or multi-nucleated Reed–Sternberg (RS) cells [2,3] embedded in an inflammatory microenvironment.

HL has been divided into classical HL (cHL), which accounts for 95% of all cases, and the less frequent nodular lymphocyte predominant HL form (NLPHL), considered a different disease.

Although originating from B-lymphoid cells, HRS cells have lost their B cell-phenotype and show a very unusual co-expression of markers characteristic for other hematopoietic lineages [4,5]. HRS cells are characterized by the constitutive activation of nuclear factor kappa B (NF-κB), the Activator Protein-1 (AP-1), the deregulation of lineage-specific transcription factors such as E2A [5], and the Interferon regulating factor (IRF)5 that, together with NF-κB activation, seems to determine the inflammatory phenotype of HRS cells [6]. HRS cells express CD30 and CD40, two members of the tumor necrosis factor (TNF)/nerve growth factor (NGF) receptor family, and in the majority of cases CD15 (75–85%) and IRF4 [5]. CD20 is positive in approximately 30–40% of cases.

Epstein–Barr virus (EBV) is causally associated with approximately one third of cases in socioeconomically developed countries, while in pediatric HL in Central and South America, the association can be up to 90% [7]. In patients with AIDS, EBV-infected HRS cells are present in nearly all cases [8].

According to World Health Organization, four histological subtypes of cHL have been distinguished based on HRS morphology and microenvironment composition: nodular sclerosis (~80% of cases), mixed cellularity (~15%), the less common lymphocyte-rich cHL and lymphocyte-depleted cHL [9].

Clinical and preclinical evidence suggests that HRS cells need the presence of a protective microenvironment to survive. For example, when HRS cells metastasize into non-lymphoid organs they need to rebuild their peculiar microenvironment. In addition, consistent with the low number of HRS cells with respect to normal cells in tumors, the prognostic significance of positron emission tomography (PET) positivity, *used to* determine the stage of *cHL*, seems to be related to the reduction of the microenvironment rather than of tumor cells [10].

Thus, tumor microenvironment (TME) interactions in cHL and their role in promoting tumor growth, immune escape and drug resistance were and will be the topic of numerous studies since they may suggest new prognostic factors and therapeutic approaches.

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cHL microenvironment composition

HRS cells represent about 1% of the tumor mass, but through efficient organization of the abundant surrounding immune cells, they are able to generate a highly aggressive and potentially lethal malignancy. The cHL microenvironment is composed by numerous small CD4-positive T cells and a variable number of eosinophils, histiocytes/macrophages, B-cells, mast cells, plasma cells, fibroblasts, mesenchymal stromal cells (MSCs) and endothelial cells (Fig. 1). HRS cells are often in close contact with small CD4+ T-cells (the so-called rosetting-T cells) expressing CD40L [11,12], while in HIV-associated cHL, T-cells are replaced by spindle-shaped CD163+ rosetting macrophages [13]. T cells represent the main component of the cHL tumor microenvironment. The greater part of them are CD4+ T helper 2 (Th2) cells and the immunosuppressive regulatory T cells (Treg), with the lack of CD4+ T helper 1 (Th1), CD8 cytotoxic T cells and NK cells. CD4+ T cells can interact with tumor cells through CD40, CD80 and CD54 [14], likely protecting them from the effects mediated by T cytotoxic or natural killer cells. Thus, the conclusion may be that the Th-cell compartment is Th2 and Treg enriched, providing some explanation for the failed immune response. However, recent studies found a predominance of Th1 over Th2 cells, an absence of markers of senescence, an excess of central memory cells (CMs), and retained cytokine secretory and proliferative capacity for cHL-associated T cells in cHL TME [15]. CHL-derived Th cells express Th1-associated CXCR3/CCR5 receptors and TNF-α/IFN-γ;/Interleukin-2 (IL-2) and less Th2-associated CCR3/CCR4, with no IL-4/IL-13. They lack exhaustion-/suppression-associated PD1 but express CD30L and CD40L and other activation markers, suggesting that TME is composed by activated T cells, likely involved in HRS cells survival/proliferation [12,16,17], rather than exhausted or immunosuppressive T cells [15]. Thus, the consolidated view of a TME composed by Th2 and immunosuppressive Treg cells likely deserves new studies.

Epstein–Barr virus (EBV) infection correlates with an increased number of Treg cells [18] and of T regulatory type 1 cell (Tr1), another type of CD4+ T cell with immunosuppressive functions [19].

The cHL TME contains a great number of fibroblasts, MSCs and a collagen-rich extracellular matrix (ECM) [20]. The abundance of eosinophils and mast cells found in cHL tissues [21] was associated with poor prognosis, even if these results have not been clearly confirmed [1].

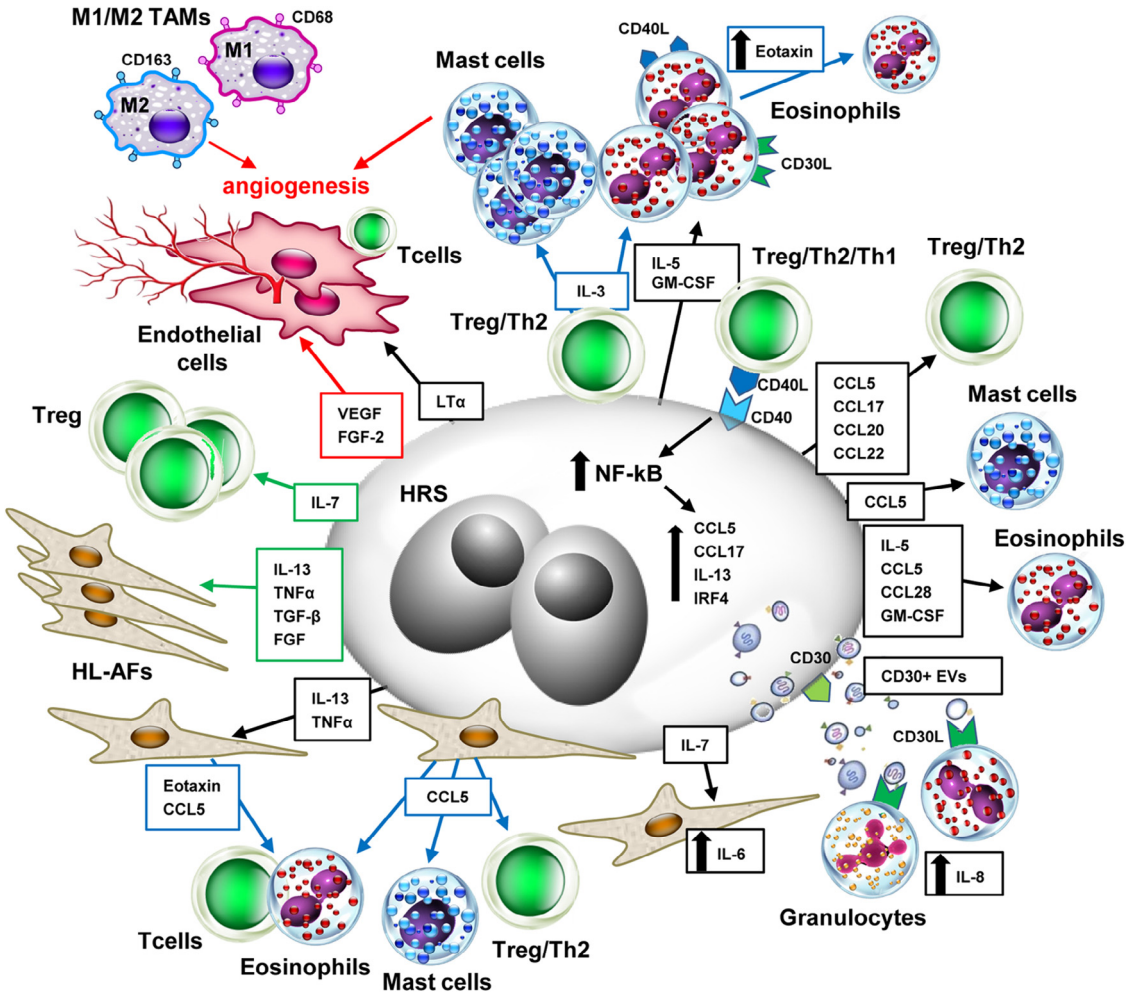

Fig. 1. A schematic representation of the Tumor-Hosts symbiosis in cHL. Molecules directly or indirectly involved in the recruitment and/or proliferation/activation of cells constituting the TME. Normal cells may be recruited by cytokines/chemokines produced by HRS cells or by "normal cells" activated by HRS cells. HRS cells may induce proliferation and/or differentiation of TME cells. HRS cells, macrophages and mast cells may contribute to angiogenesis. HRS cells may communicate with distant sites through EVs. Green arrows, cell proliferation induced by HRS cells; black arrows, direct recruitment/activation by HRS; blue arrows, recruitment/proliferation (indirect) of inflammatory cells by TME cells activated by HRS cells; red arrows, angiogenesis induced by HRS or TME cells. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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