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Review

The microenvironment in classical Hodgkin lymphoma: An actively shaped and essential tumor component

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ABSTRACT

Classical Hodgkin lymphoma (cHL) is characterized by a minority of tumor cells derived from germinal center B-cells and a vast majority of non-malignant reactive cells. The tumor cells show a loss of B-cell phenotype including lack of the B-cell receptor, which makes the tumor cells vulnerable to apoptosis. To overcome this threat, tumor cells and their precursors depend on anti-apoptotic and growth stimulating factors that are obtained via triggering of multiple membrane receptors. In addition, tumor cells shape the environment by producing a wide variety of chemokines and cytokines. These factors alter the composition of the microenvironment and modulate the nature and effectiveness of the infiltrating cells. The attracted cells enhance the pro-survival and growth stimulating signals for the tumor cells. To escape from an effective anti-tumor response tumor cells avoid recognition by T and NK cells, by downregulation of HLA molecules and modulating NK and T-cell receptors. In addition, the tumor cells produce immune suppressive cytokines that inhibit cytotoxic responses. In this review the relevance of the microenvironment in the pathogenesis of cHL will be discussed.

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1. General background on classical Hodgkin lymphoma

Hodgkin lymphoma (HL) is a distinctive disease with a characteristic clinical presentation and it was the first lymphocyte malignancy to be described [1]. It has an incidence rate of 3 per 100,000 person years and is among the most common cancers in adolescents and younger adults. About 50% of the HL patients are diagnosed between ages 15 and 35 years and a second incidence peak can be observed in the elderly [2]. HL primarily involves lymph nodes and has a unique histomorphological presentation with a minority of neoplastic cells, which generally comprise less than 1% of the total cell population, and a large majority of non-malignant reactive immune cells (Fig. 1). HL has been divided into classical HL (cHL), which accounts for 95% of all cases, and the less common nodular lymphocyte predominant HL form, which is considered to be a different disease entity.

The tumor cells in cHL are named Hodgkin and Reed–Sternberg (HRS) cells and they express diagnostic markers CD30 and usually CD15. The HRS cells are characterized by a very large (sometimes lobated) nucleus with little DNA condensation, one or more very large nucleoli, a large Golgi apparatus and much cytoplasm. This typical morphology indicates that the HRS cells are strongly activated and produce a large amount of proteins.

The origin of the HRS cells has been controversial for a long time because the immunophenotype of these cells is strikingly different from other hematopoietic cells. Detection of somatically mutated monoclonal immunoglobulin gene rearrangements indicated a germinal center B-cell origin in the majority of the cases [3,4]. However, at the time of diagnosis, HRS cells have virtually lost their B-cell identity as they show no expression of the B-cell receptor (BcR), and no or strongly reduced expression of many common B-cell markers and B-cell transcription factors [5,6]. Remarkably, they have often retained their professional antigen presenting cell phenotype including expression of the molecules necessary for antigen presentation, co-stimulation and cell adhesion [7].

In 20–40% of cHL cases in the western world, monoclonal infection with Epstein Barr virus (EBV) is present in HRS cells and this is considered to be a tumor-initiating factor. EBV+ cHL patients show a latency type II infection pattern that is restricted to expression of latent membrane protein 1 (LMP1), LMP2 and EBV-related nuclear antigen 1 (EBNA1). LMP1 and LMP2 are oncogenes that mimic CD40 activation and BcR signaling respectively [8,9].

Based on growth pattern, morphology of the HRS cells and the composition of the background infiltrate, cHL is divided into four histological subtypes, of which nodular sclerosis (~80%) and mixed cellularity (~15%) are the most common subtypes. Lymphocyte depleted and lymphocyte rich subtypes are relatively

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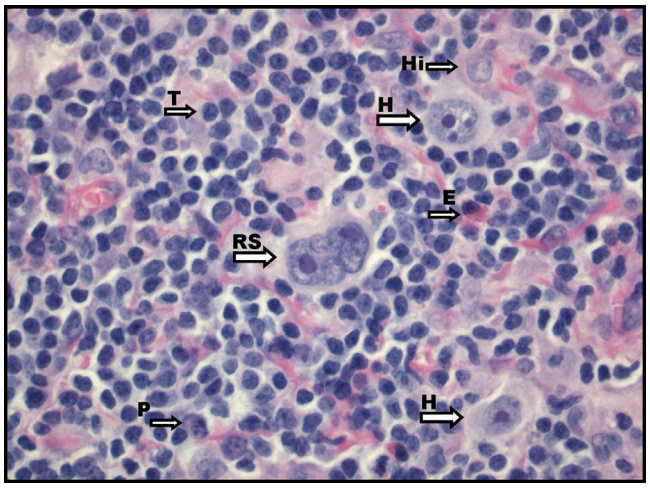

Fig. 1. Hematoxylin and eosin staining of a cHL case showing the typical tumor cells and the cellular infiltrate seen in cHL. Indicated in the image are typical mononuclear Hodgkin (H) cells and a binucleated Reed–Sternberg (RS) cell. The reactive infiltrate consists of a vast majority of small lymphocytes, usually T-cells (T), eosinophils (E), plasma cells (P) and histiocytes (Hi).

uncommon. A nodular growth pattern, sclerotic bands and large HRS cells define the nodular sclerosis subtype. In mixed cellularity HL the growth pattern is diffuse, without sclerosis and somewhat smaller, often binucleated HRS cells. In virtually all cases the microenvironment contains numerous small T-cells with variable numbers of eosinophils, histiocytes/macrophages, B-cells, plasma cells and sometimes neutrophils (Fig. 1). In mixed cellularity this microenvironment tends to be more mixed, usually with loose or granulomatous collections of histiocytes. Regardless of subtype, the tumor cells are usually in intimate contact with small CD4+ T-cells. This can be seen in tissue sections as a layer of lymphocytes directly surrounding single tumor cells (so-called rosettes) [10].

cHL can be considered an extreme model of how the tumor microenvironment impacts cancer pathogenesis. Much research has been focused on the cross talk between HRS cells and the microenvironment and its (potential) functional relevance. However, there are no cHL animal models in which cross talk between HRS cells and the microenvironment can be studied. In addition, primary tissue derived HRS cells usually do not survive in culture. This hampers the possibilities to do functional studies that closely mimic the in vivo situation. Functional studies are usually done in cHL cell lines and/or specific subsets of the reactive infiltrate. Caution should be taken in interpreting putative autocrine effects especially for membrane bound factors, as tumor cell–tumor cell contact is very infrequent in cHL tissue. Relevant markers are tested for expression in cHL tissue samples to support these experimental findings. In general, this is the closest approximation possible.

This review focuses on the microenvironment of cHL to show that the reactive infiltrating cells are not innocent bystander cells but an essential component of the tumor. The most accepted mechanisms with respect to enabling tumor cell driving mechanisms, shaping of the microenvironment and disabling anti-tumor immune responses will be discussed.

2. Tumor cell driving mechanisms

Due to the lack of a functional BcR, HRS cells and their precursors are dependent on anti-apoptotic and pro-survival signals from the microenvironment. This dependence most likely already exists at the initiation of the malignant transformation. Constitutive activation of the NF-κB pathway is one of the hallmarks of the HRS cells and provides the tumor cells with a strong pro-survival signal. Activation of NF-κB is achieved via multiple mechanisms, i.e. mutations of the NF-κB and JAK/STAT pathways [11] and signaling via the tumor necrosis factor receptor superfamily (TNFRSF), tyrosine kinases (TK) and cytokine receptors (Fig. 2).

2.1. Tumor necrosis factor receptor superfamily

CD30, a member of the TNFRSF (TNFRSF5), is abundantly expressed on HRS in virtually all cHL patients and on cHL cell lines [12]. CD30L is expressed on eosinophils and mast cells [13,14] and these cells can enhance proliferation of cHL cell lines [14]. CD30 overexpression as observed in HRS cells can induce NF-κB activation by itself, independent of CD30L [15,16]. CD40, another member of the TNFRSF (TNFRSF8), is also highly expressed on HRS cells and cHL cell lines [17,18]. Triggering of CD40 results in activation of the NF-κB pathway in HL via proteolysis of TRAF3 [19]. The CD40 ligand (CD40L) is mainly expressed on CD4+ T-cells that are present in the close vicinity of the HRS cells [18]. CD40 stimulation enhances colony formation of cHL cell lines and this effect is enhanced by IL-9 in some cHL cell lines [20]. In EBV+ cHL cases the EBV derived LMP1 acts as a constitutively activated CD40 receptor [21].

Tumor-promoting effects of cells that are present in the reactive infiltrate can be enhanced by certain cytokines. CD30L expression by eosinophils increases in response to IL-5 and GM-CSF produced by the HRS cells [13]. Stimulation with CD30L and CD40L induces secretion of several cytokines, including IL-6, IL-8 (only with CD40L), TNF and LT-α and it also induces expression of ICAM-1 (CD54) [17,22]. IL-10 derived from tumor cells and T-cells enhances membrane expression of CD40L on T-cells [20]. Thus IL-10 enhances the pro-survival CD40-CD40L signaling pathway in HL. In addition to CD30 and CD40, the HRS cells also express several other members of the TNFRSF family, i.e. receptor activator of NF-κB (RANK, TNFRSF11A), CD27 (TNRSF7), FAS (CD95, TNFRSF6), CD120a and CD120b (TNFR type I and II, TNFRSF1A and 1B), CD137 (4-1BB, TNFRSF9) [23–27]. However, the functional relevance of these receptors for survival of HRS cells has not been studied in detail.

2.2. Tyrosine kinase family members

TKs and receptor tyrosine kinases (RTKs) are important regulators of inter- and intracellular signaling and regulate cellular processes such as proliferation, differentiation and survival. CHL cell lines aberrantly express certain RTKs as compared to normal B-cells and B-cell non-Hodgkin lymphoma. HRS cells express PDGFRA in HRS cells in 75% of the patients, whereas DDR2, EPHB1, RON, TRKB and TRKA are expressed in HRS cells in at least 30% of the patients [28]. These RTKs are activated in HRS cells and can be detected as phosphorylated forms in cHL tissue. RTK activation is probably induced by binding of ligands, since there are no activating mutations in the RTKs in cHL cell lines. Collagen type 1 (ligand of DDR2) and Nerve growth factor (NGF; ligand of TRKA) are expressed by infiltrating reactive cells indicating a possible paracrine activation, whereas PDGFA (ligand of PDGFRA) is expressed by the tumor cells indicating a possible autocrine activation [28]. EphrinB1 (ligand of EPHB) is also expressed by the HRS cells, but autocrine signaling is unlikely since the receptor and its ligand are both membrane bound. The receptor for hepatocyte growth factor (HGF), c-Met, is a RTK that is expressed by HRS cells in the majority of the cHL patients [29,30]. Expression of HGF by CD21+ dendritic-reticulum cells and in 20% of the patients also by the HRS cells indicates both paracrine and autocrine activation of c-Met+ HRS cells [29,30]. Inhibition of c-Met suppresses cell growth by blocking the cells in the G2/M phase. Thus, c-Met acts as an oncogene, providing growth advantage for the HRS cells [29,30]. Activation of RTKs results in activation of signal transduction pathways, such

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