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STAT-6 In Hodgkin Lymphoma Pathobiology and Treatment-Review of The Literature

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1. Abstract

Classical Hodgkin Lymphoma (cHL), consists of rare neoplastic Hodgkin and Reed-Sternberg cells (HRS) residing in a prominent inflammatory background. HRS show deregulated activation of multiple signaling pathways and transcription factors. The activation of these pathways and factors is partly mediated through interactions of HRS with various other types of cells in the microenvironment, but also through genetic lesions. Signal transducers and activators of transcription (STAT) are a family of transcription factors that regulate a broad range of cellular processes, such as proliferation, differentiation, and survival, in a large variety of cell types. STAT6 pathway is activated as a response to the binding of cytokines IL-4 and IL-13 to their receptors on the cell membrane. The ability of activated STAT6 to promote lymphoproliferation and the requirement for STAT6 in normal cytokine-induced cell proliferation provides a strong rationale for further study of STAT6 in cHL.

This review outlines the current evidence on the role of STAT6 in cHL. We report on the findings concerning the involvement of STAT6 in the pathogenesis, as well as in the cross-talk between tumor cells and their microenvironment. The dependency of HRS on micro environmental interactions and on deregulated STAT6 signaling pathway may offer novel strategies for targeted therapies.

3. Introduction

Hodgkin lymphoma (HL) was recognized in the first half of the 19th century by Thomas Hodgkin and Samuel Wilks [1,2]. It is one of the most common lymphomas in Western World. Its annual incidence is 3 cases per 100.000 persons. Neoplastic tissues usually contain a small number of scattered large mononucleated and multinucleated tumor cells (designated Hodgkin and Reed-Sternberg cells or HRS cells) residing in an abundant heterogeneous admixture of non-neoplastic inflammatory and accessory cells. The latter includes lymphocytes, especially Th2 cells, monocytes, granulocytes, eosinophils, mast cells and histiocytes [1,3,4]. Biological and clinical studies in the last decades have shown that Hodgkin lymphomas are comprised of two disease entities: nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL). Based on the consistence of the microenvironment, the latter one is divided into four subtypes: nodular sclerosis (80%), mixed cellularity (15%), lymphocyte rich (5%) and lymphocyte depleted (<1%) (1, 5, 6). The immunophenotypic and genetic features of the mononuclear and multinucleated cells are identical in these histological subtypes, whereas their clinical features and association with EBV show differences.

In Ebstein-Barr virus (EBV) positive cases evidence suggest its role in the pathogenesis of HRS cells [5,7-11]. The prevalence of EBV in HRS cells varies according to the histological subtype and epidemiologic factors. The highest frequency is found in mixed cellularity classical HL and the lower incidence in nodular sclerosis classical HL (WHO 2008). EBV is found in 40% of cases in Western world, however may be seen in up to 90% of cases in Central and South Africa [5].

Classical HL is a monoclonal lymphoid neoplasm derived (in most instances from B cells). Despite their derivation from germinal center B cells, HRS have lost much of the B-cell specific expression program and have acquired B-cell inappropriate gene products. In addition, deregulated transcription factors in classical HL promote proliferation and abrogate apoptosis in the neo plastic cells. Multiple signaling pathways, mainly including nu-

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clear factor kappa-B (NF-κB), Janus kinase-signal transducer and activator of transcription signaling (JAK/STAT), PI3K-Akt and ERK, have deregulated activity in HRS cells. Coherently, recurrent genetic alterations detected in HRS cells of cHL frequently affect members of the NF-κB or JAK/STAT signaling pathways [5,8,10,12]. CHL is associated with over expression and an abnormal pattern of cytokines and chemokines including IL-5, IL-6, IL-7, IL-9, IL-10, IL-13 and granulocyte-macrophage colony-stimulating factor and/or their receptors in HRS cells [13-17] which likely explain the abundant admixture of inflammatory cells, fibrosis and the predominance of Th2 cells in the infiltrating T-cell population [18].

STAT-6 is a protein that belongs to a family of transcription factors known as STATs. STAT6 is one of the seven members of STAT protein family (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6), which was identified and cloned for the first time by two independent teams [19]. The signaling cascade of the JAK-STAT pathway is triggered by the engagement of cytokine receptors. This leads to the activation of docking domains for STAT monomers. After having bounded to the phosphotyrosines of their receptors the STATS themselves are being phosphorylated on tyrosine residues, which enables them to form dimers. The active STAT dimers translocate to the nucleus, where they control the expression of target genes [20].

There are only few publications regarding STAT6 in HL. STAT6 activation in cHL is mediated by IL-13, and this has been proved by immunohistochemistry, immunoblotting, Western blotting and ELISA. Notably, co-expression of IL-13 and its receptor IL-13Rα1 is characteristic for HRS cells [21-24].

The current treatment of HL is based on multi-drug chemotherapy, radiation therapy (25, 26) and autologous or allogenic stem cell transplantation in case of recurrence [26]. Recent studies provided insights into deregulation of key nodal signaling pathways, including the PI3K [27], NF-κB [28-30] and JAK/STAT [31] pathways, which are amenable to small-molecule targeting. Understanding how neoplastic cells interact and depend on their microenvironment has led to a remarkable new step in developing new treatment strategies targeting not only the malignant tumor cells but also the tumor microenviroment [25,26].

In this context, the present review outlines the current evidence on the role of STAT6 in cHL. Molecular, and histopathological data regarding STAT6 expression in neoplastic cells are presented along with the possible involvement in pathogenesis, and pathobiology of cHL. In addition, the current evidence for its potential use as a therapeutical target is discussed.

4. STAT-6

The signal transducers and activators of transcription (STATs) including STAT6 are latent cytoplasmic proteins that undergo tyrosine phosphorylation by Janus kinases (JAKs) in response to cytokine exposure in the extracellular milieu. Ligation of cytokines interleukin-4 (IL-4) and interleukin-13 (IL-13) with their receptors result in a common STAT6-mediated signaling pathway critical for a number of responses in T cells, including the development of T helper type 2 (Th2) cells and IL-4-stimulated proliferative responses, functions that were demonstrated through the analysis of mice with disrupted Stat6 alleles [32-34]. Once phosphorylated, STAT6 is transported to the nucleus where it regulates gene expression in various cell types critical to the balance between host immune defense and inflammatory responses [35,36]. IL-4, IL-13, and STAT6 promote humoral immunity, clearance of helminthic parasites as well as the pathogenesis of allergic disorders like asthma, food allergies, and atopic dermatitis [37-39].

While STAT6 is required for normal immune function, it has been also implicated in numerous malignancies including prostate and colon cancer [40-42], glioblastoma [43], lymphoma [21,44,45], and leukemia [46,47]. A recurrent intra-chromosomal rearrangement on chromosome 12q leading to the formation of a NAB2–STAT6 fusion oncogene has been recently identified in solitary fibrous tumor [48,49]. As a result, nuclear expression of the cytoplasmic transcription factor STAT6 is found in solitary fibrous tumor and serves as a useful diagnostic marker [50, 51]. Using Fluoresence In Situ Hybridization (FISH) analysis, Doyle et al detected STAT6 amplification in a subset of dedifferentiated liposarcoma with nuclear immunoexpression of STAT6 protein [52]. STAT6 amplification has also been demonstrated in Hodgkin lymphoma cell lines [53]. Currently, experimental therapeutics that target the IL-4/IL-13/STAT6 pathway are being tested in clinical trials [54, 55]. The involvement of STAT6 in human oncogenesis is opening up new possibilities regarding the study and identification of new molecular targets for the development of future cancer therapy.

5. Stat6 and Hodgkin Lymphoma

5.1. Stat6 In Pathogenesis and Tumor Growth

The malignant cells in cHL (HRS cells) arise from the germinal center cells or the immediate post germinal center cells. Although originating from B-lymphoid cells, HRS cells have lost their B cell-phenotype and show co-expression of markers characteristic for other hematopoietic lineages [5,56]. 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, determine the inflammatory phenotype of HRS cells [57]. 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].

The JAK/STAT signaling pathway represents another key pathway in pathogenesis of HL. STAT3, STAT5 and STAT6 are activated and expressed at high level in HL [21, 58]. Given that the activation of docking domains for STAT monomers is due the activation of JAK/STAT pathway, the expression of STATs and especially of STAT6 in HRS cells might represent a possible biomarker of JAK/STAT activation in tissue specimens. Clinicopathological studies correlating clinical data and molecular results with immunohistochemical expression of STAT6 protein, could further investigate this possibility.

Epstein–Barr virus (EBV) is causally associated with approximately one third of HL cases in socioeconomically developed countries, while in pediatric HL in Central and South America, the association can be up to 90% [59]. In patients with AIDS, EBV-infected HRS cells are present in nearly all cases [60]. Different studies have shown that Epstein-BarrVirus contributes to the transformation of its precursors, as well as the survival and proliferation of the malignant HRS cells [4,5,7]. The EBV+ HRS cells typically show an EBV latency II gene expression profile, meaning expression of the viral proteins EBV nuclear antigen 1 (EBNA1) and latent membrane proteins 1 and 2a (LMP1 and LMP2a) [61]. The EBV-encoded LMP-1 is a viral mimic of the CD40 receptor, and by constitutive signaling it activates potently the nuclear factorκB, c-Jun N-terminal kinase, and phosphatidylinositol 3-kinase pathways.LMP-1 has been reported as a viral oncoprotein promoting tumor growth but also apoptotic resistance and immune modulation [9,62,63]. Recently, demonstrated that the induction of LMP-1 by IL-4 and IL-13 is mediated by STAT6 and a newly defined high-affinity STAT6-binding site in the LMP-1 promoter in HL-derived, EBV-converted KMH2-EBV cell lines [10]. This evidence strongly supports the role of STAT6 in the pathogenesis of EBV-positive cHL. Furthermore, it indicates that inhibition of the interactions between the cytokines and its specific receptor or inhibition of the STAT6 signaling pathway might have beneficial effects in the EBV-positive cases by down-regulating the expression of LMP-1.

In respect to tumor growth, it has been proved that survival and proliferation of HRS cells is dependent on STAT3 and STAT6 activation, since rescission of their activation by neutralizing antibodies, JAK/STAT blockers or siRNAs against STAT3 and STAT6 reduced proliferation and induced cell death in vitro [14, 25, 64]. In addition. pointed out the association between antibody-mediated neutralization of IL-13, reduced STAT6 phosphorylation and decreased HL cell proliferation [19].

Interestingly, Baus et al. [55] demonstrated that knockdown of STAT6, by using constantly expressed shRNAs against STAT6 by lentiviral transduction, induced apoptotic cell death in the cHL cell lines L428 and L1236cHL. In the latter study, the values of the G1 and G2 cell populations were not affected, suggesting that STAT6 has a strong effect on cell survival and does not provoke cell-cycle arrest.

The above data suggest that STAT6 promotes the neoplastic proliferation and consequently it might represent a possible therapeutic target.

5.2 Stat6 and Hl Microenvironment

Unlike any other neoplasm, the tumor in cHL is made predominantly of the non-neoplastic HRS cells rather than the neoplastic HRS cells, which often constitute no more than 1-3% of the entire mass [12]. CD4+ T cell lymphocytes are the most abundant cell type in cHL, clustering around the RS cells [48], and the overproduction of helper T cell type 2 (Th2) cytokines and chemokines such as interleukin (IL)-13, IL5 and eotaxin [14] is reported in most cases. The great number of cytokines produced in cHL by HRS cells promote neoplastic cell growth and survival. At the same time, the secreted molecules are implicated in the reactions between the cells of microenvironment and trigger an abnormal immune response to the HRS cells while support them to overcome the antitumor activity of cytotoxic T and NK cells [8]. This is highlighted by expression or secretion of PD-1 ligand, galectin-1 and IL-13 which directly interfere with the functional activity of T cells, primarily polarize specific T cell subsets towards a regulatory phenotype, or prevent an effective Th1-response [65-68].

Early studies reported that IL-13 and IL-13R (alpha)1, the IL-13-specific receptor chain, are frequently expressed by HL-derived cell lines as well as by HRS cells from biopsy material of tissues involved by HL. Furthermore, antibody-mediated neutralization of IL-13 in cultures of HL-derived cell lines resulted in a dose-dependent inhibition of proliferation, and it was associated with increased apoptosis and with significant decreases in both cellular proliferation and levels of phosphorylated STAT6 of HL cell lines [13, 14, 69].

These data support the hypothesis that STAT6 is involved in cellular interactions that modify the tumor microenvironment which, on the other hand, regulate the immune response against tumor cells. Since HRS survival seems to be mostly due the activated proliferating and proinflammatory cytokine secreting cells [8, 70], the IL-13/STAT6 signaling, involved in micoenvironmen-

tal interactions, may be an additional target for new therapeutic approaches.

5.3. Stat6 and Therapy of Hl

The majority of patients with HL are treated with a combination of multi-drug chemotherapy and radiotherapy. Despite relative success of therapy, approximately 20% of patients will not be cured with the current available therapy and the disease will relapse [26]. Moreover, 30-35% of patients with high-risk prognostic features will not be treated [71]. Additionally, patients recurring after autologous and/or allogenic stem cell transplantation are regarded incurable and are considered to have a median survival <3 years [72]. Hence, the development of novel therapeutic agents are needed for patients with refractory or relapsed disease.

Novel therapeutic strategies focus on the special and unique pathology and microenvironment, the deregulated signaling pathways, as well as the induction of anti-HRS cell immunity by modulating the microenvironment. Among the latter, the immune checkpoint inhibitors (e.g. programmed cell death 1/PD-1, PD1-Ligand/PDL-1) have been proved a breakthrough therapy for advanced HL [66, 73, 74].

The JAK/STAT pathway is activated in HL as a result of genomic amplification of JAK2 and/or inactivating mutations in an inhibitor of JAK activity, SOCS1 (75). A proof of the therapeutic potential of JAK inhibitors has been proved by a phase I study of the JAK inhibitor SB1518, a selective inhibitor of JAK2 and FLT3. In this study, 14 out of the 34 patients had cHL. Of these 14 patients, 6 patients had a steady disease with the treatment [31]. Have also supported the positive effects of SB1518, a novel macrocyclic pyrimidine-based JAK2 inhibitor for the treatment of HL. More specifically, SB1518 aims the JAK/STAT pathway by inhibiting tyrosine phosphorylation on JAK2 (Y221) and downstream STATs. Hence, SB1518 has probably an anti-proliferative effect on lymphoid cell lines, driven by mutant or wild type JAK-2 or FLT3. The latter results from cell cycle arrest and induction of apoptosis [31].

Furthermore, JAK inhibitors can lead on propitious immunomodulary effects. Derenzini et al. [76] showed that AZD1480, JAK 1/2 inhibitor exhibited immunomodulary effects at low concentrations by down regulating the expression of Th2 cytokines and chemokines (Il-13 and TRAC), as well as STAT3-mediated reduced expression of PD-L1 and PD-L2, which take part in immune escape mechanisms in HL. In addition. Demonstrated that JAK2 inhibition by the selective inhibitor, fedratinibdecreased phosphorylation of JAK2, STAT1, STAT3, and STAT6 and reduced the expression of additional downstream targets, including PD-L1, Interestingly, the phosphorylation of STAT 1, 3 and 6 was inhibited by chemical JAK2 blockade in a 9p24.1 copy number-dependent manner in cHL cell lines [20].

Recently presented a JAK 1 /2 inhibitor, ruxolintinib, which reduced the phosphorylation of STAT3 and STAT6, as well as the expression of c-Myc in the HL cell line HDLM-2. These results were amplified when ruxolintinib was combined with the Bcl-2/Bcl-xL inhibitor, Navitoclax, or with anti-CD30 toxin conjugate, brentuximab vedotin (BV). The combination of ruxolitinib with Navitoclax or BV alone prolonged survival period but did not cure HDML-2 tumor-bearing mice. On the other, BV combined with ruxolitinib and/or with Navitoclax led to sustained complete remission in this model of HL. The studies above propose future use of the combination of BV with ruxolitinib in patients with HL [77].

The significance of STAT6 inhibition in HL therapy has been reported. The authors demonstrated a direct antiproliferative effect of histone deacetylase (HDAC) inhibitor vorinostat on HRS which was associated with cell cycle arrest and apoptosis and an immune mediated effect by altering cytokine and chemokines secretion in the microenvironment due to inhibition of STAT6 phosphorylation [78]. Furthermore demonstrated that the pan-deacetylase inhibitor panobinostat has potent antiproliferative activity against Hodgkin lymphoma-derived cell lines. At the molecular level, panobinostat activated the caspase pathway, inhibited STAT5 and STAT6 phosphorylation, and down-regulated hypoxia-inducible factor 1 α and its downstream targets, glucose transporter 1 (GLUT1) and vascular endothelial growth factor.

In respect to STAT6 signaling, have shown that specific blocking of the IL-4 and IL-13-mediated STAT-6 activation by an IL-4 binding fusion protein APG598 or an IL-4R antagonist APG201 (R121D/Y124D) make HL cells more prone to apoptotic effect by chemotherapeutic drugs such as Mitomycin C, 5-Fluoracil, Etoposide, Doxorubicin and Plaxicatel. This outcome is based on the inhibition of STAT-6 mediated elevation of expression of the anti-apoptotic Bcl-2 family protein Bcl-xL. Thus, the IL-4/Il-13-STAT6-Bcl-xL pathway may be a crucial target for HL treatment [25]. In addition, Demonstrated that treatment of two IL-13-responsive HL-derived cell lines, with Soluble interleukin-13Ralpha2 decoy receptor, resulted in the inhibition of cell proliferation, and down-regulated the phosphorylation of STAT6 [24]. All the data investigating the correlation of STAT6 with cHL and its prognosis are summarized in **Table 1.**

Table1. Presentation of studies regarding STAT6 in Classical Hodgkin Lymphoma.

Reference	STAT-6 relatedremarks	Association withprognosis
Skinnider*etal.* 2002	STAT-6 activation in cHL is mediated by IL-13	Negativeassociationwithprognosis
Skinnider*et al.* 2002, Hinz*et al.* 2002	STAT-6 is activated and expressed at high levels in HL	Negativeassociationwithprognosis
Kiss*etal.* 2011	STAT-6 plays an important role in the pathogenesis of EBV-positive cHL	Negativeassociationwithprognosis
Skinnider*et al.,* 2002 Natoli*et al.,* 2013 Diaz*etal.,* 2011	Survival and proliferation of HRS cells is dependent on STAT-6 and STAT-3 activation	Negativeassociationwithprognosis
Skinnider*etal.*, 2002	Antibody-mediated neutralization of IL-13 reduced STAT-6 phoshporylataion and decreased HL cell proliferation	Positiveassociationwithprognosis
Hart*etal.* , 20011	JAK-STAT inhibitors seem to have a therapeutic potential	Positiveassociationwithprognosis
Hebenstreit*etal.*, 2016	JAK2 selective inhibition decreases phosphorylation of STAT-6 and reduces the expression of downstream targets.	Positiveassociationwithprognosis
Buglio*etal.*, 2008	Histone Deacetylase (HDAC) inhibitors decrease STAT-6 phosphorylation and promote cell cycle arrest and apoptosis	Positiveassociationwithprognosis

6. Conclusion

In conclusion, although the complexity of interactions between HRS cells and their microenvironment and their functional role during malignant transformation is not completely understood, however, emerging data indicate that STAT6 is involved in cHL pathogenesis and growth, through interplay with cellular signal transduction pathways. Experimental results following disruption of microenviromental interactions by STAT6 inhibition generate optimism for novel therapeutic strategies for HL, possibly including drugs that block specifically the STAT6 signaling pathway and particularly the STAT6 protein.

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