Leptin and Lymphoma

Subjects: Oncology

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Obesity is a risk factor for many different types of cancer including lymphoma. Since hyperleptinemia is one of the mechanisms of pathophysiology of obesity such as inflammation.

lymphoma obesity leptin

1. Leptin Signaling in Lymphoma

The metabolic abnormalities associated with an excess of adipose tissue include biochemical alterations such as high levels of plasma triglycerides [1] or peripheral insulin resistance, which lead to increased levels of insulin and glucose [2]. Importantly, other factors closely involved in obesity have been described as promoters of many diseases in the last decades, such as the adipokines leptin or adiponectin. Leptin is known to activate and promote the proliferation of monocytes and lymphocytes by activating JAK-STAT, PI3K, and MAPK [3][4]. Leptin signaling also drives the activation of many oncogenic pathways leading to the increased proliferation, epithelial-mesenchymal transition, migration, and invasion of tumor cells [5]. Specifically, leptin signaling pathways can promote lymphomas (**Figure 1**). Leptin binds its receptor LEPR-b to transduce activation signals into cells via JAK2, which is phosphorylated together with Tyr^{985}, Tyr^{1077}, and Tyr^{1138}. STAT3 proteins bind phospho-Tyr^{1138} and are phosphorylated and translocated into the nucleus of dimeric units, activating the transcription of their targeting genes and leading to a huge variety of lymphomas, including DLBCL, unclassifiable diseases with features between DLBCL and Burkitt lymphoma, mantle cell (MCL), NK/T-cell (NKTCL), peripheral T-cell (PTCL), anaplastic large cell (ALCL) or intestinal T-cell lymphomas, as well as HL [6][7]. One of its targeting genes, the suppressor of cytokine signaling (*SOCS)-3*, has been found to be highly expressed in FL and ALCL [8][9]. Similarly, STAT5 binds phospho-Tyr^{1077} and is translocated into the nucleus after its phosphorylation, thus promoting not only DLBCL, PTCL, MCL, or HL (as STAT3 signaling does) but also γδ-T-cell and lymphoblastic lymphomas [10][11][12][13][14][15].

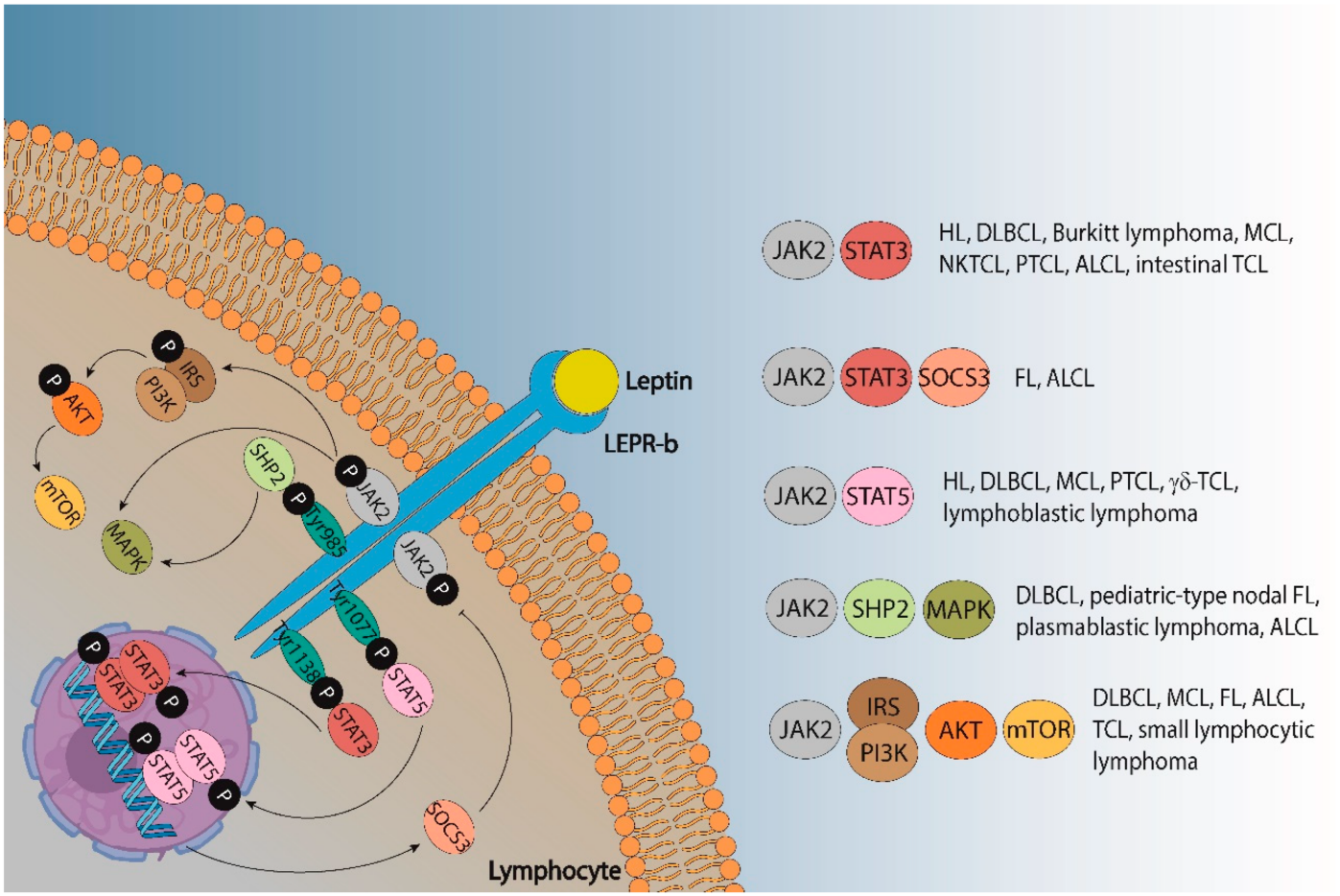

Figure 1. Leptin signaling pathways that could promote different types of lymphoma. ALCL—anaplastic large cell lymphoma; DLBCL—diffuse large B-cell lymphoma; FL—follicular lymphoma; HL—Hodgkin lymphoma; MCL—mantle cell lymphoma; NKTCL—natural killer/T-cell lymphoma; PTCL—peripheral T cell lymphoma; TCL—T-cell lymphoma.

Moreover, SHP2 binds to phospho-Tyr^{985} and promotes the activation of the MAPK pathway, although leptin can also activate MAPK signaling independent of SHP2. The protein SHP2 has been associated with ALCL [16][17], whereas MAPK activity impairs outcomes in DLBCL, pediatric-type nodal FL, and plasmablastic lymphoma [18][19][20]. The phosphorylation of JAK2 also promotes the PI3K/AKT/mTOR signaling pathway via IRS activation. The IRS proteins are a family of cytoplasmic adaptor proteins with important roles in cancer [21]. Regarding lymphomas, IRS-1 has been demonstrated to activate anaplastic lymphoma kinase (ALK), which is involved in ALCL [22], and IRS-4 could mediate the mitogenic signaling of LB cells: a murine pre-T-cell lymphoma [23]. The activation of the PI3K/protein kinase B (AKT)/mammalian target of the rapamycin (mTOR) pathway also plays a key role in lymphoma, and many signaling pathway inhibitors have been developed to treat FL, DLBCL, MCL, small lymphocytic, and T-cell NHL [24][25][26][27][28].

At the cellular level, leptin signaling favors Th1 responses by enhancing IL-2, interferon (IFN)-γ synthesis, and inhibiting IL-4 production, which suggests that this adipokine may alter T-cell responses toward a proinflammatory phenotype [29][30]. The recruitment of proinflammatory cytokines by leptin could regulate the production of adhesion

molecules, such as the vascular cell adhesion molecule (VCAM)-1 and intercellular cell adhesion molecule (ICAM)-1 [31][32], that have been found to be highly increased in newly diagnosed lymphoma patients and correlate with tumor dissemination, the aggressiveness of the disease, and worse response to treatments [33][34][35][36].

Leptin also induces TNF-α in many settings [37][38][39]. Although its role in cancer remains controversial (as previously explained), TNF-α has been shown to play a key role in the pathogenesis of NHL [40] and may increase the risk of disease together with leptin, especially in FL [41] and DLBCL, through polymorphisms in the *TNF rs1800629G>A* gene [42]. Additionally, TNF-α levels were higher in lymphoma from children compared with their solid-tumor counterparts [43], which suggests the relevant role of this protein in lymphomas. IL-10 and IFN-γ released by leptin may be implicated in lymphomagenesis since their circulating levels were increased in patients with BMI ≥ 25 kg/m^2 compared to individuals with a lower BMI [44]. Although IL-10 may be associated with a higher risk of NHL, especially FL, IFN-γ was not associated with that risk [41]. The risk of lymphoma in patients with a higher BMI could be also increased by the release of IL-6 via leptin signaling [44], but it still needs to be completely elucidated since other studies did not find this association [41]. Of note, blood glucose was suggested as a prognostic biomarker for TCL [45], and the human oocyte testis gene 1, an antigen whose disruption promotes aberrant glucose homeostasis and defective hormone secretion, has been shown to decrease levels of insulin and leptin in TCL-bearing mice [46].

2. Leptin and LEPR Genes in Lymphoma

Leptin has been suggested to promote immune dysfunctions regarding body weight regulation and NHL: mainly DLBCL and FL. Regarding gene expression, lymphomas are mainly characterized by mutations that involve genes, such as B-cell lymphoma (*bcl)-2* [47], *bcl-6* [48], *p15* and *p16* [49], *p53* [50], or *myc* [51], which have been widely considered as biomarkers of poor prognosis in those diseases [52][53][54][55][56][57][58]. Specifically, BCL-2 is an antiapoptotic protein that belongs to the BCL-2 family together with other proteins, including (but not limited to) CL-X_L and BCL-W, with antiapoptotic properties, as well as the proapoptotic BAX, BAK, or BID proteins [59]. Leptin signaling has been demonstrated to play a key role in B-cell homeostasis through the induction of Bcl-2 [60], which could increase the risk of different pathological conditions. Leptin has demonstrated the ability to inhibit apoptosis and induce cell cycle by elevating Bcl-2 and cyclin D1 in leptin-receptor-deficient (*db/db*) mice [60]. Similarly, the Bcl-2 protein expression was elevated in db/db mice with diabetes [61][62][63], Which may be predisposed to develop lymphoma [64]. This adipokine also decreased the apoptosis of myocardial cells in rats via bcl-2 [65] and reduced the apoptosis of beta cells at physiological concentrations in vitro by maintaining or up-regulating bcl-2 expression, which could promote non-insulin-dependent diabetes mellitus [66][67]. Additionally, mild maternal protein deprivation during lactation in rat pups could affect thymic homeostasis by increasing the activity of leptin, which improves the levels of BCL-2 and inhibits the apoptosis of thymocytes [68]. In human trophoblasts, leptin also prevents apoptosis when elicited with high temperatures by increasing the BCL-2/BAX ratio [69]. In cancer, the silencing of leptin in HeLa cells, a cervical cancer cell line, has reduced the expression of bcl-2 and, consequently, promotes apoptosis and inhibits cell proliferation, thus suggesting the probable role of leptin in the progression of cervical cancer [70].

Those notions are especially significant since NF-kB, STAT3, PI3K, and AKT pathways are activated in lymphoma cells via leptin/LEPR signaling [71][72][73] and improving bcl-2 expression.

Several studies have analyzed the role of leptin genes in lymphomas (**Table 1**). Single nucleotide polymorphisms (SNPs) in leptin genes *LEP 2548GA and LEP 2548AA* have been shown to increase the risk of FL compared with *LEP 2548GG* [74]. Specifically, genetic polymorphisms in *LEP 2548GA* have been significantly associated with NHL under the homozygous co-dominant model and additive genetic model in the Caucasian population rather than among Asians after analyzing almost 7000 cases and 8000 controls [75]. The positive associations between *LEP 2548GA* and the susceptibility of NHL were also found in another study, but without statistically significant differences [76]. Moreover, SNPs in *LEP 2548GA* have not been suggested to increase the risk of cutaneous T cell lymphomas (TCL) but may be involved in the pharmacogenetic of different treatments for this disease since patients with AG or GG genotypes (with lower plasma leptin levels) could better respond to topical steroids (male patients) and phototherapy (female counterparts) compared with AA patients [77].

Table 1. *Leptin/LEPR* gene polymorphisms analyzed in lymphomas. NHL—non-Hodgkin lymphoma; DLBCL—diffuse large B-cell lymphoma; FL—follicular lymphoma.

Reference	Type of Study	*Leptin/LEPR* Genes	Conclusions
[78]	Case-control	*LEP 19AG, LEP 2548GA, LEP 2548AA, and LEPR Q223R*	Polymorphism in *LEP 19AG* increased the risk of DLBCL and FL. Genetic interactions in *LEPR 223RR*, *LEP 2548GA*, or *LEP 2548AA* genes also increased the risk of NHL.
[74].	Case-control	*LEP 2548GA, LEP 2548AA,* LEP *19AA, and* LEPR *223Q>R*	Obesity was associated with risk of NHL, especially DLBCL. The risk of NHL was increased by *LEP 2548GA* and *LEP 2548AA* genes and decreased by *LEP 19AA*, particularly in men younger than in 45 years olds with FL. Conversely, no associations were found between lymphoma risk and *LEPR 223Q>R*.
[77]	Case-control	*LEP 2548GA*	Cutaneous T-cell lymphoma patients with leptin genes involving AG or GG genotypes may respond better to topical steroids and phototherapy.
[75]	Meta-analysis	*LEP 2548GA*	Gene polymorphism may increase the risk of NHL, particularly in the homozygote co-dominant model and the additive genetic model of Caucasian populations.
[79]	Meta-analysis	*LEP 19AG*	Gene polymorphism was associated with lower NHL risk under the homozygous codominant model, recessive genetic model (especially among the Latin American population), and additive genetic model.
[80]	Meta-analysis	*LEPR Q223R*	Gene polymorphism did not affect the risk of NHL, although it may be significantly increased in Asian and

Reference	Type of Study	*Leptin/LEPR* Genes	Conclusions
			African individuals.
[76]	Meta-analysis	*LEP 2548GA, and LEP 19AG*	LEP 2548GA polymorphism increases NHL susceptibility and LEP 19AG is associated with a decreased risk of NHL, especially FL.
[81]	Meta-analysis	*LEP 19AG*	LEP 19AG may decrease the risk of NHL, especially in Asians, Caucasians, and mixed populations.
[42]	Case-control	*LEPR rs1327118G>C, and LEP rs2167270G>A (LEP 19AG)*	LEP rs2167270 G>A polymorphism was associated with the decreased risk of DLBCL in the recessive mode models among the Jordanian Arab population. [42][76]

reported that genetic polymorphisms in the *LEP A19G* gene were associated with a lower risk (or even decrease in the risk) of NHL among Latin American individuals [79] and Asians, Caucasians and mixed populations [81]. Additionally, polymorphisms in the *LEP A19G* receptor, *LEPR Q223R*, could not increase the susceptibility of NHL [80]. Other leptin genes, such as LEP 19AA, could decrease that risk [74], whereas the leptin receptor gene *rs1327118 G>C* has not been associated with susceptibility to the disease [42].

By contrast, the ghrelin GHRL SNP allele for *GHRL 4427G>A* has been inversely correlated with the risk of NHL, especially DLCL [82]. GHLR and leptin are hormones that play antagonistic roles in controlling energy balance [83] by increasing and decreasing the levels of neuropeptide Y (NPY), respectively [84][85]. NPY is a powerful appetite stimulator that serves as an immune mediator by releasing and inhibiting proinflammatory cytokines [82]. The role of NPY in disease risk and progression remains unclear since it has been found that NPY genes may affect the risk of NHL, especially FL [82], but no significant changes in NPY levels after treatment have been revealed in patients with different types of cancer, including NHL [40].

3. Serum Leptin and LEPR Expression in Lymphoma

Similar to leptin genes, the relationship between the concentration of circulating leptin or LEPR expression and lymphomas has also been studied (**Table 2**). It has been demonstrated that leptin levels increase the risk of NHL in individuals with BMI ≥ 25 kg/m^2 [44]. In addition, the phosphorylation of STAT3 and AKT via JAK2/STAT and PI3K/AKT signaling pathways has led immunohistochemical studies to reveal high expressions of LEPR, p-STAT3, and p-AKT in many DLBCL cases [73]. In line with this notion, leptin has been demonstrated to stimulate the proliferation of DLBCL cells and inhibit apoptosis via the PI3K/AKT signaling pathway in vitro, whereas the pretreatment of DLBCL cells with LEPR-specific siRNA or the inactivation of PI3K/AKT activity depleted these responses [72]. Likewise, leptin has increased the cell viability of CTL MOLT-3 cells by promoting the recruitment and expression of Glut1, and LEPR-siRNA, which inhibited those responses [86].

Table 2. Leptin/LEPR levels or expression analyzed in lymphomas.

Reference	Type of Study	Leptin/LEPR Levels or Expression	Conclusions
[87]	Case study	All patients: 23 (0–310) pg/mL. CR patients: 25 (0–310) pg/mL. PD patients: 21.5 (0–140) pg/mL.	Leptin levels were similar regardless of the response to treatment.
[40]	Case-control	Article not available *	After treatment, BMI, body weight and body fat mass decreased significantly. Also, low leptin levels were found before and after treatment compared with controls.
[88]	Case-control	Lymphoma patients: 16.4 ± 10.4 ng/mL. Controls: 10.3 ± 7.6 ng/mL.	Leptin levels were positively correlated with BMI but were not high in lymphoma patients at diagnosis.
[89]	Case-control	Patients: 6.0 ± 6.31 ng/mL. Controls: 5.9 ± 7.3 ng/mL.	There was no association between leptin levels and NHL in children.
[90]	Case-control	Patients: 8.2 ± 7.26 ng/mL. Controls: 7.5 ± 8.3 ng/mL.	There was no association between leptin levels and HL in children.
[72]	Case study	High LEPR expression in 39.8% of DLBCL patients	LEPR overexpression could be associated with DLBCL carcinogenesis via PI3K/AKT pathway. Also, leptin/LEPR signaling promoted the proliferation of DLBCL cells in vitro.
[91]	Case-control	Pre-treatment: 5.3 ± 1.56 ng/mL. Post-treatment: 9.8 ± 2.7 ng/mL. Controls: 6.7 ± 1.2 ng/mL.	Leptin levels were significantly lower in patients than in controls and increased in patients who achieved remission.
[41]	Case-control	Patients: 8.5 (3.8–17.1) ng/mL. Controls: 10.6 (5.2–21.8) ng/mL.	Serum leptin levels were significantly associated with NHL risk at diagnosis, but predicted a lower risk of FL.
[73]	Case-control	High LEPR expression in 45% of DLBCL patients	LEPR may promote JAK/STAT and PI3K/AKT signaling pathways and induce the phosphorylation of STAT3 and AKT, which may be involved in the prognosis of DLBCL.
[86]	Cases	Higher LEPR expression in tissues of T-cell lymphoma patients (58.3%) and in all cell lines, especially in MOLT-3 and Jurkat cell lines	LEPR overexpression was positively correlated with Glut1 expression. TCL MOLT-3 cell line demonstrated that leptin stimulated cell glucose uptake via promoting the recruitment and expression of Glut1.
[44] [40]	Case-control	Patients: 4182.30 ± 246.95 pg/mL. Controls: 4782.00 ± 193.65 pg/mL	Leptin levels were significantly higher in women than in men and in obese patients compared with their non-obese counterparts, which increased the risk of NHL.

NHL adult

l with the international prognostic index in NHL [88], suggesting a paradoxical role of leptin that has been previously explained not only in cancer [92] but also in other settings [93][94][95]. Also, Bertolini et al. (1999) studied patients with NHL (mainly DLBCL and FL but also other types of lymphomas such as MCL, PTCL, ALCL, large granular NK-cell

lymphoma, extranodal marginal zone lymphoma of MALT), whose leptin levels were not only similar regardless of the tumor but were also not correlated with age, gender, or event-free survival [87].

NHL—non-Hodgkin lymphoma; DLBCL—diffuse large B-cell lymphoma; FL—follicular lymphoma; * Article not available to check overall survival. The information was taken from the abstract.

4. Linking Leptin, Lymphoma, and Obesity

Most of the studies have analyzed the relationship between leptin and lymphoma, obesity and lymphoma, or obesity and leptin. Therefore, only a few studies have analyzed the possible associations among leptin, lymphoma, and obesity. Recently, leptin has been positively associated with BMI and NHL risk [44]. Also, patients who survived the Burkitt type, non-Burkitt, and lymphoblastic lymphomas not only had low leptin levels but also a normal/low BMI (19.5 ± 3.4 kg/m^2) [96]. On the other hand, leptin levels have been positively correlated with BMI but not associated with lymphoma risk [88]. Similarly, relationships between leptin or BMI with HL or NHL were not found in pediatric patients [90]. A BMI ranging from underweight to healthy values in children newly diagnosed with HL or NHL has been positively correlated with leptin. Thus, leptin levels were low in those patients at diagnosis [89][91] but may significantly increase after remission and predict the response to treatment or progressive disease [91]. Regarding SNP, it has been found that leptin gene polymorphisms were independent of BMI and did not alter the risk of NHL [74].

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