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REVIEW

Mechanisms underlying the association between obesity and Hodgkin lymphoma

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Abstract A solid body of knowledge indicates that overweight and obese subjects are prone to develop cancer, aggressive disease, and death more than their lean counterparts. While obesity has been causally associated with various cancers, only a limited number of studies beheld the link with classical Hodgkin lymphoma (HL). Contemporary meta-analysis and prospective studies confirmed the association of body mass index with HL. Besides epidemiological evidence, excess adiposity is known to influence tumor behavior through adipokines, adipose-derived stem cell migration, and metabolism regulation, and by modulating immunoinflammatory response. Nevertheless, the obesity paradox has been described in few cancers. Considering that adipose tissue is an immunomodulatory organ, and that inflammation is the cornerstone of HL pathophysiology, the rationale for being causally related due to endocrine/paracrine interactions cannot be negligible. In this hypothesis-generating review, we explore the biologically plausible links between excess adiposity and HL in light of recent basic and clinical data, in order to create a basis for understanding the underlying mechanisms and foster applied research. The establishment of an association of excess adiposity with HL will determine public health preventive measures to fight obesity and eventually novel therapeutic approaches in HL patients.

Keywords Obesity · Bone marrow adipocytes · Hodgkin lymphoma · Tumor microenvironment

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Introduction

Obesity has been described as a cause of morbidity and mortality in type 2 diabetes, dyslipidemia, cardiovascular diseases, and cancer [1]. The estimated number of deaths caused by cancer will duplicate until 2030 as result of the obesity epidemic [2]. The association between obesity and many cancer types has been consistently established [3]. In Hodgkin lymphoma (HL), a contemporary meta-analysis on prospective studies established a significant association between body mass index (BMI) and HL [4]. Concordantly, a recent prospective study in over 1 million individuals demonstrated an increased risk for HL by 10 kg m^{-2} units of increase in BMI [5]. Whereas epidemiologically obesity seems to be associated with HL, the biological rationale and mechanisms behind this causal relation remain largely unexplored.

Hodgkin lymphoma is characterized by an inflammatory microenvironment at the tumor site in lymph nodes [6, 7]. The

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distinctive HL's malignant Hodgkin and Reed-Sternberg (HRS) cells reciprocally interact with the surrounding milieu conceding tumors' survival and evasion advantages [6, 7]. Although the exact cause of HL remains unknown, age, familial and viral infections, clinico-pathological markers, immunosuppression, and metabolic response kinetics have been identified as predictors of disease [8, 9]. Noteworthy, despite the high cure rate, in advanced stage disease approximately 25 to 30 % of patients are not cured with standard therapeutic regimens alone and about 15–20 % of patients still die after relapse or disease progression [9, 10]. In advanced stages, where bone marrow infiltration may occur [11], the international prognostic score and other risk stratification instruments remain only modestly effective to predict disease progression and therapeutic response [9, 12].

Excess adiposity is associated with chronic inflammation; hence, excess adiposity-mediated inflammation may play a role in promoting HL growth and survival [13]. Moreover, the accumulation of immune cells in HL, including T and B cells, neutrophils, eosinophils, and mast cells, might be disturbed by excess adiposity, which is known to modulate the immune system function [14]. Adding to immunoinflammatory derangements, there is a systemic metabolic dysfunction in obesity that stimulates altered circulating levels of adipokines. Actually, some of these molecules have been associated with HL [15–17]. Notwithstanding that the mechanisms behind the causally invoked association between obesity and HL continues unsettled, supportive biological rationale supports plausibility for the relation of adipose tissue/inflammation/HRS axis with HL risk and aggressiveness. Together, these obesity-linked endocrine and paracrine mechanisms may shape the microenvironment for growth and spread of HRS malignant cells. Moreover, albeit still experimentally unproven in HL, it is expected that the known paracrine action of adipocytes within the bone marrow microenvironment [18, 19] might modulate HRS cell behavior.

Obesity epidemic estimates for the next years encourage a previously unmet need to clarify the biological mechanisms involved in the association between excess adiposity and HL, fostering development of novel markers and potential therapeutic targets. Furthermore, the identification of local effects of bone marrow adipocytes in invading HL cells might improve understanding, making advanced stage of disease more manageable.

Hodgkin lymphoma pathophysiology: lessons to uncover new mechanisms

Hodgkin lymphoma's pathologic hallmark is the presence of Hodgkin and Reed-Sternberg cells within a reactive cellular background [6, 20]. These unique features of HL are far outweighed by reactive and stromal cells [7]. In fact, survival, proliferation, and immunoinflammatory mechanisms have an important role in HL pathophysiology [6, 21].

Hodgkin lymphoma's tumor microenvironment, particularly the pattern of cytokines/chemokines secreted by HRS cells and non-neoplastic surrounding cells, may influence HL growth and progression [7, 22]. Among others, HL microenvironment is modulated by autocrine and paracrine actions of interleukins (ILs) (e.g., IL-1α, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-13), chemokines (thymus- and activation-regulated chemokine or CCL17, and macrophage-derived chemokine or CCL22), macrophage colony-stimulating factor (M-CSF), tumor necrosis factor-α (TNF-α) and β (TNF-β), transforming growth factor beta (TGF-β), soluble CD30, and chitinase-3-like protein 1 (YKL-40), with autocrine tumor growth effect [22, 23]. Among these, thymus- and activation-regulated chemokine (TARC) and macrophage-derived chemokine (MDC) are partially responsible for whittling the HL microenvironment, by inducing Th2 and Treg cells [22], which has been associated with reduced immunosurveillance [24]. Likewise, altered signaling pathways involve cytokine receptors (e.g., IL-2R, IL-6R, IL-9R, IL3R), macrophage colony-stimulating factor receptor (M-CSFR), tumor necrosis factor receptors (TNFR1, TNFR2), and CD30 and CD40 [25, 26]. Recently, the downstream signaling through the IL-3/IL-3R pathway was shown to induce growth and survival of HL cells [27]. Paracrine signals may arise from non-malignant tumor-infiltrating cells in the HL microenvironment (e.g., B cells, T cells, natural killer cells, eosinophils, mast cells, neutrophils, and histiocytes/macrophages) [6, 28]. Notably, also the nuclear factor-kappa B (NF-kB) and Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathways have been identified in HL [7]. Epstein-Barr virus (EBV) influences the activation of the NF-kB pathway, which is involved in the expression of multiple anti-apoptotic factors and pro-inflammatory cytokines and reduces the expression of CD99, a marker associated with HRS cell phenotype [29]. This cell surface receptor is involved in T-cell adhesion, leukocyte migration, and T-cell caspase-independent cell death, playing also a role in the induction on human thymocyte T-cell receptor (TCR) and on major histocompatibility complex (MHC) class I and II expression. It has been reported that CD99 deficiency leads to the arrest of MHC class I molecules at the Golgi complex, impairing their transport to the cell surface, which constitutes one of the most frequent immune escape mechanisms adopted by cancer cells [30]. Some authors identified candidate-circulating biomarkers for HL, with prognostic and/or predictive response to therapy. These molecules act at the HL site and modulate disease outcome [31–33]. Furthermore, it was found that before treatment, HL patients have increased levels of serum interleukin 6 (IL-6) and YKL-40, both correlated with disease progression stage [15].

Infiltrating cells are attracted by cytokines and chemokines and interact with HRS cells using the CD30 ligand [34]. Similarly, recruited fibroblasts are responsible for tumor tissue fibrosis and for the production of cytokines and chemokines. This complex crosstalk further enhances the recruitment of more cellular components to the microenvironment [35]. This biology provides a strong rationale for investigating factors that influence immunoinflammatory unbalances and regulate migration and homing of cells towards the tumor microenvironment, as is the case for excess adiposity.

The genetic profiling of HL has been for a long time hampered by the scarcity of neoplastic cells within a large amount of surrounding reactive cells. Recent developments have demonstrated alterations at chromosomal, gene copy number, and epigenetic levels [36]. Interestingly, while gene mutations render constitutively active NF-kB and JAK/STAT signaling pathways [37, 38], epigenetic modulators such as the microRNA-155 overexpressed by HRS cells may contribute to loss of B-cell identity [39].

There is longstanding recognition of a relation between HL and EBV. However, it remains debatable whether it is a primary causation, a contributor to pathogenesis, or associated with prognosis of HL [13, 23].

Obesity and Hodgkin lymphoma

Obesity is currently considered epidemic worldwide [40]. Overweight and obesity are defined as excessive accumulation of adipose tissue and are associated with increased risk of morbidity and premature mortality. Besides other related diseases, epidemiological studies reported obesity as a risk factor for cancer [3, 41, 42]. In the USA, the estimated risk of death from cancer in morbidly obese (BMI ≥40 kg/m^2) was 1.5 in men and 1.6 in women [41], whereas in Europe, obese have 1.5 to 3.5 higher risk of having cancer [2]. Alongside, it has been estimated that approximately 30 % of cancer deaths might be related with dietary and behavioral factors, namely, high BMI, low intake of fruits and vegetables, lack of exercise, smoking, and alcohol abuse. A recent meta-analysis based on prospective studies in over 1 million individuals reported an increased risk in development of HL for obese subjects (BMI ≥30 kg/m^2) and for each 10-kg/m^2 units of increase in BMI, respectively [4, 5]. Indeed, a number of studies reported a positive association of obesity with hematologic malignancies, including HL [5, 42–47], even though others have not found such an association [48–54]. Despite the batch of positive association studies between obesity and HL, it is important to highlight the time when the anthropometric assessments were made and the outcomes considered. Indeed, some authors consider that this potential protective effect of lower BMI in cancer may be due to the effects of cancer-related cachexia, which is more deleterious than the potential adverse events related to a higher BMI [55]. Noteworthy, two studies found that obese and overweight patients had a better prognostic profile [49, 51]. Obesity may increase the risk for developing HL, even though its effects in survivors might be paradoxal, thus influencing the natural history of disease [56].

Specifically in HL, the intake of saturated fats, which is also related with excess adiposity, can modulate the immune function through an anti-apoptotic action on T cells and increased expression of pro-inflammatory molecules [57]. Nevertheless, most studies rely on body mass index measures and World Health Organization BMI-based classification of obesity, which are imperfect estimates of adiposity and disease risk [58–60] and do not account for local fat depots (e.g., visceral adipose tissue). These depots were shown to have adverse specific adipokine expression profiles, contributing towards more aggressive tumors [61–63]. Future epidemiological studies should address these issues by using more precise methods (e.g., visceral and subcutaneous fat determinations by computed tomography scan, whole body fatness by tetrapolar bioimpedance, or local and whole body fat measurements through magnetic resonance imaging, among others) to evaluate whole and local body fatness in association with HL.

At present, the adipocyte is no longer considered a passive component of the human metabolism. It is known as an endocrine/paracrine organ that exerts many biological effects, through production of growth factors, cytokines, chemokines, and hormones [64]. These biologically active molecules secreted primarily, partially, or exclusively by adipocytes, known as adipokines, have a significant role in regulating tissue angiogenesis and tumor growth [65]. In fact, the importance of the interaction between cancer cells and the surrounding stroma cells has been increasingly accepted. These interactions are particularly prominent in environments rich in adipocytes [66]. The excess body fatness is characterized by a chronic low-grade inflammatory state with altered circulating levels of adipokines, including IL-6, IL-8, leptin, adiponectin, TNF-α, vascular endothelial growth factor (VEGF), osteopontin (OPN), haptoglobin (Hp), and YKL-40, among others [67–69] (Fig. 1). These molecules impact cancer cell-related mechanisms such as proliferation, apoptosis, and migration [70, 71]. In this context, the evaluation of markers related to obesity and immune response in HL might reveal new opportunities for understanding the mechanisms responsible by the association between obesity and HL. Various adipokines have already been shown to be linked with HL risk and with advanced stage of disease, namely, IL-6 and interleukin 7 (IL-7) [15, 16, 72], while others endure as promising targets for future studies (e.g., leptin, adiponectin, resistin, HGF, visfatin, etc.). Thus, the chronic inflammation sustained by expanding the adipose tissue may modulate the host immunosurveillance [14] and exert a direct effect on both local tumor microenvironment and distant tumor cells, through the systemic effects of paracrine signals (Fig. 1).

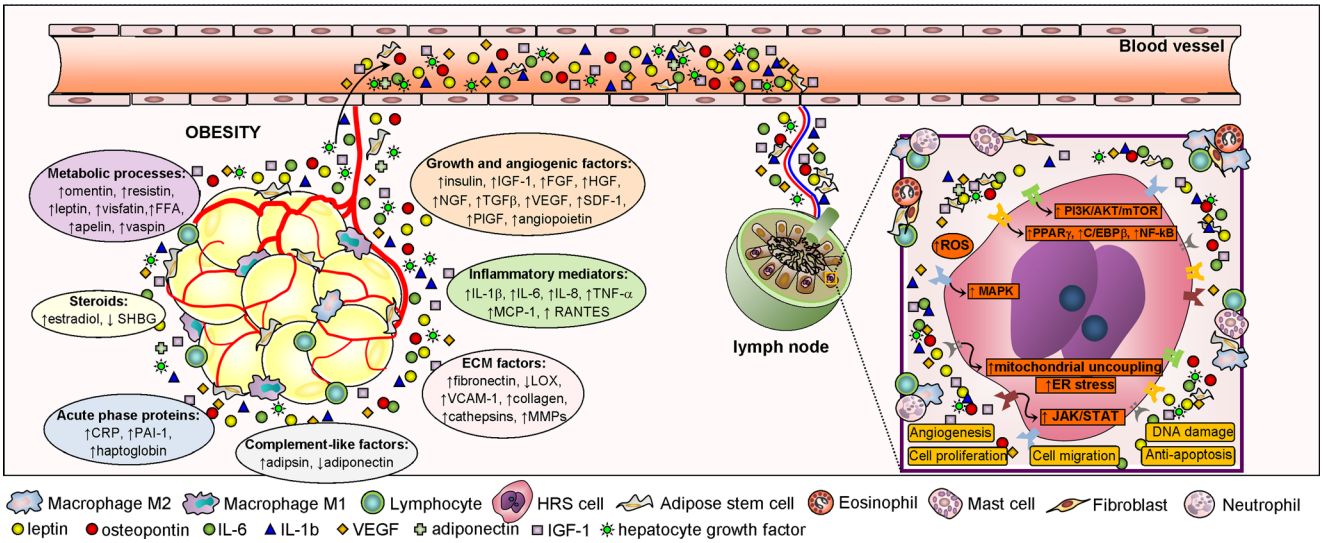

Fig. 1 Endocrine effects of obesity impact Hodgkin Reed-Sternberg lymphoma cells. Excess adiposity modulates HRS aggressiveness in lymph nodes through a systemic effect mediated by adipokines and migrating adipose stem cells. In obesity states, the adipose tissue acquires the following characteristics, hypertrophied adipocytes, neoangiogenesis with increased vessel density, infiltration with M1 type macrophages, increased amount of adipose stem cells, and upregulated secretion of pro-tumoral adipokines, whereas anti-tumoral adipokines are downexpressed (e.g., adiponectin, SHBG, and LOX). The *full black arrow* represents adipokines and adipose stem cells entering peripheral blood. The circulation levels of these adipokines are significantly increased in obese (as opposed to adiponectin levels), reaching lymph nodes, where they may induce either direct effects to HRS cells through direct binding to cell receptors or indirect actions by interaction with cells in the microenvironment modulating their crosstalk with HRS cells. Ultimately, adipokines may induce intracellular signaling pathways (represented by *solid black arrows* within HRS cell) and mechanisms that will lead to angiogenesis, and to cell proliferation, cell migration, DNA damage, or anti-apoptosis of HRS cells. *AKT* Akt kinase, *C/EBPβ* CCAAT/enhancer binding protein beta, *CRP* C-reactive protein, *ER* endoplasmic reticulum, *ECM* extracellular matrix, *FGF* fibroblast growth factor, *FFA* free-fatty acids, *HGF* hepatocyte growth factor, *HRS* Hodgkin Reed-Sternberg cell, *IGF-1* insulin-like growth factor-1, *IL-1β* interleukin 1 beta, *IL-6* interleukin 6, *IL-8* interleukin 8, *JAK* Janus kinase, *LOX* lysyl oxidase, *mTOR* mammalian target of rapamycin, *MMP* matrix metalloproteinase, *MAPK* mitogen-activated protein kinase, *MCP-1* monocyte chemoattractant protein 1, *NGF* nerve growth factor, *NF-kB* nuclear factor kappa B, *PAI-1* plasminogen activator inhibitor-1, *PI3K* phosphatidylinositol 3′-kinase, *PlGF* placental growth factor, *PPARγ* peroxisome proliferator-activated receptor gamma, *RANTES* (CCL5) regulated on activation normal T cell expressed and secreted, *ROS* reactive oxygen species, *SHBG* sex hormone binding globulin, *STAT* signal transducer and activator of transcription, *SDF-1* stromal derived factor 1, *TGFβ* transforming growth factor beta, *TNF-α* tumor necrosis factor alpha, *VCAM-1* vascular cell adhesion molecule 1, *VEGF* vascular endothelial growth factor

Angiogenesis is a well-established hallmark of tumor development both in solid tumors and hematological malignancies (including HL). Reasonable data, mostly supported by retrospective immunohistochemistry evaluations, stands for a relevant role of angiogenesis in HL. In this pathology, a shift towards an angiogenic phenotype is observed as a result of an unbalanced angiogenic versus anti-angiogenic stimulus [73]. Interestingly, many of the adipokines overexpressed by the adipose tissue in obese individuals are well known for their potent pro-angiogenic effects [67]. Therefore, it seems plausible that these adipokines might mediate the causally invoked association between excess adiposity and HL, through a modulatory effect in angiogenesis (Fig. 1).

Besides adipokine secretion, the expanding adipose tissue is also infiltrated by macrophages ongoing M2-to-M1 differentiation, further contributing towards the obesity-associated systemic chronic inflammation and insulin resistance [74, 75] (Fig. 1). Leptin and adiponectin, hormones exclusively produced by adipocytes, and with opposing effects in obesity and cancer, contribute to the polarization of macrophages with a pro-inflammatory phenotype [76] and towards anti-inflammatory M2 [77], respectively. Interestingly, in HLs, the presence of $CD68^{+}$ tumor-associated macrophages indicates poor prognosis [20, 78] and higher adiponectin levels were found in pediatric HL patients [79]. Recently, the soluble circulating CD163 and TARC were identified as possible biomarkers of HL [31]. Also interestingly, CD163 is a known marker for M2 macrophage polarization and a receptor for Hp, which is a major acute phase protein overexpressed in conditions such as obesity and HL [80, 81]. Nonetheless, Hp is induced not only by HL-associated IL-6 downstream transcription factor STAT3 but also by hypoxia-inducible factor-1α (HIF-1α) which is overexpressed in HL [82]. Therefore, excess adiposity seems to interfere with tumor cell signaling pathways and to modulate macrophage differentiation, both of which may impact the tumor. This obesity-driven inflammatory environment exerts tumor-promoting effects, due to altering inflammation pathways implicated in cell proliferation, survival, angiogenesis, and bone invasion associated with cancer (Fig. 1). Taken together, these evidences demonstrate potential unrevealed links that should foster experimental validation in order to uncover the impact of these obesity-associated molecules in HL.

Bone marrow adiposity and Hodgkin lymphoma—adipocytes have a role in the bone marrow microenvironment?

Adipocytes in the bone marrow have been implicated as regulators of the microenvironment [18, 83], presenting a distinctive phenotype, which resembles both white and brown adipose tissue [84]. Accumulation of adipocytes in the bone marrow begins at birth, by age 25 represents approximately 70 % of the bone marrow, and continues to build up throughout life [85]. Besides representativeness, bone marrow adipocytes present a unilocular lipid morphology similar to white adipose tissue and are a unique adipose depot that overexpresses genes associated with cell differentiation and inflammation [86–88]. Amplified bone marrow adiposity due to diet-induced obesity in mice was recently implicated in altered bone metabolism and inflammation within the bone microenvironment [89]. Adiposity in bone marrow is modulated by high fat diet, diabetes, aging, dyslipidemia, and obesity, through diverse pathways that come together to regulate the expression and activity of a key pro-adipogenic transcription factor, the peroxisome proliferator-activated receptor γ2 (PPAR-γ2) [90].

Bone marrow adipocytes act as energy suppliers to bone physiological functions, including bone remodeling [83, 91]. In addition to energy storage, these adipocytes secrete adipokines and fatty acids that impact significantly the metabolism and function of other neighboring cells [85, 88]. From this interaction in bone marrow milieu, an inverse relationship has been described between osteoblastogenesis and adipogenesis, with a negative correlation of marrow adiposity with osteoblast number and bone mineral density [90]. In fact, several factors produced in the bone marrow may exert a regulatory role in local adipocytes, and adipokines secreted in marrow adipocytes might influence other cellular players through a paracrine effect [85] (Fig. 2).

Hodgkin lymphoma involving the bone marrow ranges between 2 and 32 %, with an average incidence of 10 % [92, 93]. Although the chronic low-grade inflammation and the upregulated secretory profile associated with obesity may exert endocrine effects, we should not overlook paracrine actions of adipocytes in the bone marrow microenvironment bearing HRS cells from primary HL tumors [19]. The crosstalk between adipocytes and cancer cells has been demonstrated to support progression and aggressiveness of tumors in other oncologic models [66, 94–98], as well as metastatic cell growth in the bone marrow [99]. Fat cells seem to be able to translocate stored lipids to metastatic tumor cells, ultimately driving cancer growth and motility [96, 100, 101]. The complex interaction between components of the bone marrow, including adipocytes and eventually tumor cells, is depicted in Fig. 2.

In other oncologic models, the fatty acid binding protein 4 (FABP4) was implicated in adipocyte-tumor cell interactions [96, 99]. Notwithstanding, FABP4 is transcriptionally regulated by PPARγ, a lipid chaperone that controls PPARγ [102, 103], while both seem to be involved in adipocyte-induced metabolic switching in the cancer microenvironment. Interestingly, in B lymphoma cells, the decreased PPARγ expression was related with increased proliferation and survival as well as initiation of inflammatory pathways, specifically the activation of NF-κB [104], further underlining the link between cellular metabolism and neoplastic progression.

Primary cancer-derived metastases that home to the bone are by themselves incapable of inducing bone resorption. However, these aggressive malignant cells interact with bone constituents and influence the function of bone-degrading cells (osteoclasts), inducing osteolytic lesions [105]. Bone-invasive HRS cells from HLs have been described as osteolytic [106, 107]. The complex interaction of tumor cells with the bone marrow microenvironment, including adipocytes, exerts profound influence in proteolytic degradation and bone resorption, enabling metastasis allocation. Obesity and aging are known effectors of bone remodeling by forming adipocytes instead of osteoblasts, which will lead to increased osteoclast activity and osteoporosis [85, 108]. A key enzyme for osteoclastic bone resorption is cathepsin K (CTK) which degrades the bone matrix protein collagen I and other proteins of the bone matrix [109]. CTK expression within the bone marrow milieu is high in osteoclasts and adipocytes and results in accelerated bone turnover [110, 111] and in a potential contribution to the metastatic process. CTK production was also described in cancer cells that metastasize to the bone [112, 113]. CTK acts by upregulating the processing of its substracts extracellularly, including the secreted protein acidic and rich in cysteine (SPARC or osteonectin) that interacts with collagen I and other matrix proteins to attract and anchor malignant cells in the bone [110]. In addition, VEGF, a growth factor known to be involved in tumor cell migration and in osteoclast differentiation and migration, has been proposed to be modulated in the bone microenvironment by CTK cleavage [109, 114]. Noteworthy, VEGF is produced by HRS cells and has been associated with angiogenesis and prognosis in HL [115, 116].

Besides the key role of CTK in degrading collagen I, it also seems to be relevant for adiponectin cleavage, which may be a mechanism to stimulate osteoclastogenesis via increased expression of receptor activator of NF-κB ligand (RANKL), to modulate marrow fatness or to influence adiponectin-mediated suppression of tumorigenesis [117–119]. Bone marrow adipocytes also stimulate osteoclast differentiation and activity by directly secreting RANKL [120]. Interestingly, RANK and RANKL are functionally expressed in HRS cell lines whereas RANK is expressed in primary HRS cells, in order to regulate the cellular infiltrate and cytokine and chemokine secretion in HL [121].

Bone marrow adipocytes are a significant secondary source of leptin and IL-6, whereas only trace amounts of IL-1β and

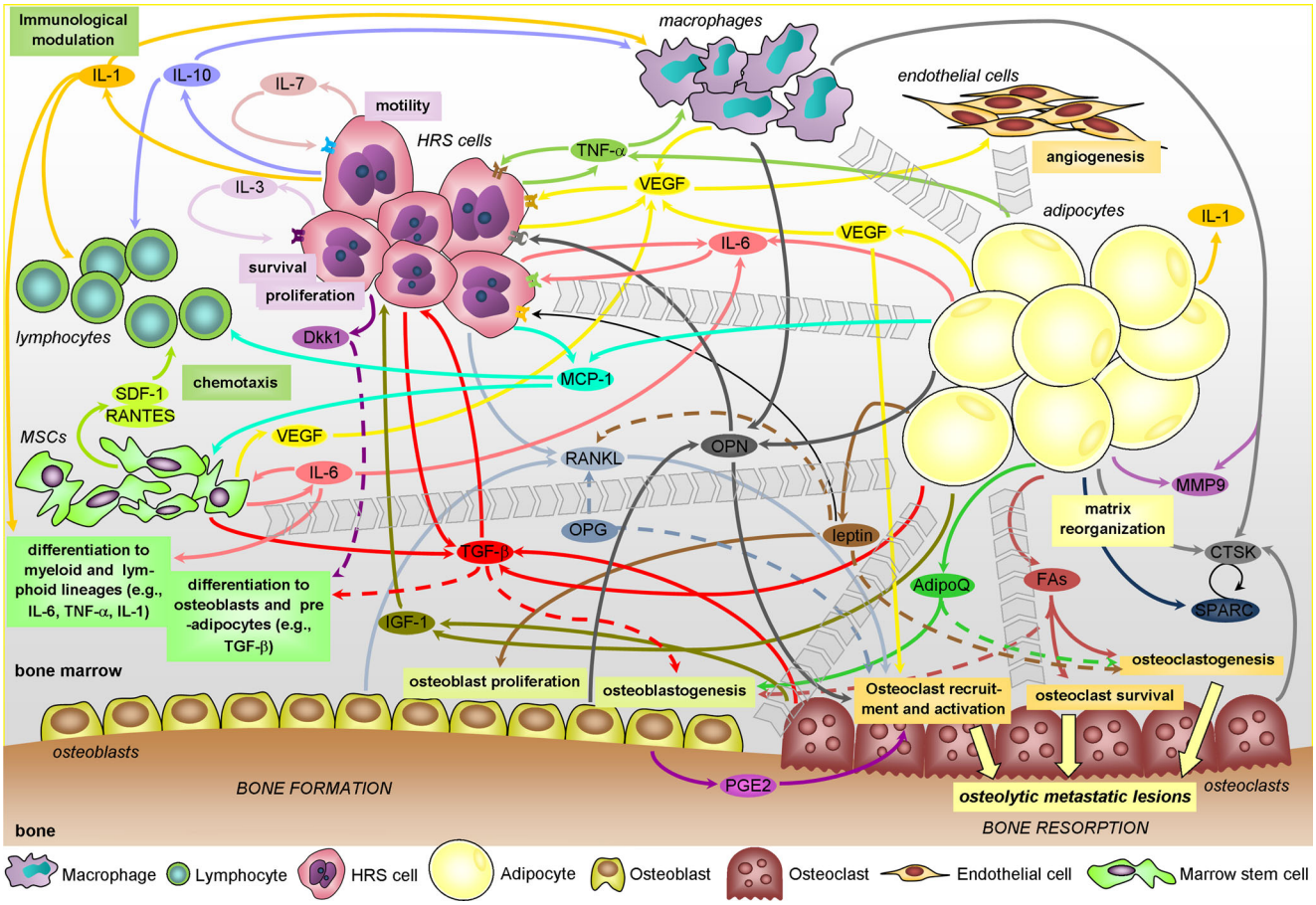

Fig. 2 Hypothetical role of obesity and adipocytes in the bone marrow microenvironment invaded by HRS cells. This figure depicts the complex interaction between cellular components in the bone marrow and its mediators, particularly the contribution of bone marrow adipocytes to bone homeostasis and metastatic progression. Most adipokines produced in adipocytes (leptin, VEGF, osteopontin, TNF-α, MMP9, IL-1, IL-6, TGF-β, IGF-1, MCP-1) may contribute either directly (through an effect in HRS tumor cells mediated by their specific receptor downstream signaling—impacting HRS cell motility, survival, and proliferation) or indirectly (by influencing other cells in the microenvironment, including osteoblasts, osteoclasts, lymphocytes, macrophages, and endothelial and mesenchymal stem cells, to acquire a pro-tumoral behavior—immunological modulation, increased chemotaxis, cell differentiation, matrix reorganization, neoangiogenesis, increased osteoclast recruitment, and activation, ultimately resulting in bone resorption and osteolytic metastatic lesions) to this stage aggressiveness and HL prognosis. *Solid black lines* with *arrows* represent secretion or the effect of a given adipokine, whereas *dashed lines* denote inhibitory action. Multiple *light yellow arrows* mean the reciprocal impact other cells might have in adipocytes. *AdipoQ* adiponectin, *CTSK* cathepsin K, *DKK-1* dickkopf-related protein 1, *FAs* fatty acids, *IL-1* interleukin 1, *IL-3* interleukin 3, *IL-7* interleukin 7, *IL-10* interleukin 10, *MMP9* matrix metalloproteinase 9, *MSCs* mesenchymal stem cells, *OPG* osteoprotegerin, *PGE2* prostaglandin E2, *RANKL* receptor activator of nuclear factor kappa-B ligand, *SPARC* secreted protein acidic and rich in cysteine

TNF-α were found [122, 123]. These molecules exert interactive regulatory mechanisms between them, in order to modulate the marrow environment, controlling the proliferation and differentiation of hematopoietic precursors as well as the maturation of stromal cells [124]. Given the importance of JAK/STAT signaling in HL malignant cells, and that leptin and IL-6 downstream signals are mediated by this pathway [125–127], we hypothesize that these adipokines might influence HRS cell survival and proliferation, both through an endocrine mechanism in lymph nodes and by a paracrine effect in the bone marrow. Since leptin and IL-6 are upregulated in the serum of obese subjects, they can partially explain the association between excess adiposity and HL. Only few unpowered studies have measured serum leptin and adiponectin levels in HL patients, mostly children, with inconclusive mixed results [79, 128, 129]. With respect to IL-6, several reports demonstrated that it was a relevant cytokine for HRS proliferation and survival and a useful biomarker of aggressiveness [130, 131]. It is largely unknown whether bone marrow adipocytes behave differently in the presence of HL malignant cells. Thus, further investigation on the interactions of bone marrow adipocytes with HRS cells is required to clarify many unanswered questions and advance knowledge with potential clinical translation.

Here, we hypothesize that when HRS infiltrate into the bone marrow, resident adipocytes may have a role in bone remodeling, yielding tumor cells with adipokines and fatty acids to boost growth and survival, concurring towards worst

prognosis. Further clinical studies should follow disease behavior in HL obese patients and evaluate the impact of intervening in obesity on HL prognosis. Therefore, obesity and its effect on bone marrow adipocytes may represent a potential therapeutic target in the future.

Future perspectives

Obese subjects are at increased risk of progression of certain cancers, as seems to be the case of HL. Knowledge of adipocyte biology in the context of malignancy is therefore crucial for understanding the pathophysiological basis of obesity associated with HL. The reprogrammed tumor-educated behavior of adipocytes likely provides a tumor-permissive metabolic, inflammatory, fibrotic, and angiogenic microenvironment that modulate HRS cells' survival.

Additionally, despite detailed evaluation of prognostic factors in HL, our knowledge of the effects of adiposity in cancer diagnosis, treatment, and survival is limited. The impact of BMI on prognosis has been studied in chemotherapy-treated patients with HL with a long follow-up. Indeed, the studies previously mentioned showed that HL patients had significantly better prognosis with higher BMI groups. From this perspective, this possible protective role of obesity in HL patients may be associated as a result of BSA-based chemotherapy in a relative "under-treatment" of normal and underweight individuals. It may also reflect the contribution of the HL microenvironment, which sustains tumor growth and survival of both HRS cells as the cells of the HL microenvironment. In this context and in light of recent evidences, therapeutic strategies in HL focus on anti-tumor strategies that alter the HL microenvironment, changing it from protective to cytotoxic, being evaluated in clinical trials [132]. Thus, in a personalized cancer therapy, obesity and bone marrow adipocytes may contribute to favorable outcomes.

Understanding the heterotypic interactions between adipocytes and HRS cells could lead to the identification of further novel targets for HL therapy. Targeting adipose tissue with anti-obesity and/or anti-diabetic agents, such as metformin and thiazolidinediones, might be a promising option to treat patients with cancer who are overweight/obese. However, despite metformin activity against cancer growth or thiazolidinediones (a class of peroxisome proliferator-activated receptor γ agonists), growth-inhibitory effects on transformed cells, so far there are neither experimental studies nor clinical trials. At a time of personalized cancer therapy, there is an unmet need for targeted therapeutic approaches for patients with obesity and cancer, including HL. Thereby, future research should focus on the manipulation of adipocyte biology (e.g., enhance adiponectin synthesis, stimulate intra-adipocyte lipid oxidation, and promote reactivation/conversion of brown adipose tissue) [133], in order to promote health and benefit patients. With a pace of discovery indicating that the adipose tissue-cancer field is rapidly growing, with new insights unfolding for many cancer types, it remains to be seen how well we will translate these discoveries into HL, and further to HL patients.

Finally, although intuitively relevant for future studies, the effects of lifestyle intervention in HL prevention and treatment are not yet clear. The impact of these interventions on weight loss also offers a means for testing the reversibility of some mechanisms triggered by obesity. Thus, research endeavor to ascertain the influence of weight loss and other lifestyle changes (e.g., physical exercise or diet) on HL risk or outcomes is both required and feasible. Randomized controlled trials including physical exercise, nutrition, or both interventions are urgently needed to guide recommendations for susceptible groups and for HL survivors and to support implementation of chemoprevention strategies and weight management programs. Indeed, the clinician-patient relationship after cancer diagnosis is an opportunity to encourage lifestyle modifications, which might impact cancer recurrence [134], risk of other diseases, and overall quality and length of life [135].

Conclusions

Although recent studies support a positive but weak causally related epidemiological association between obesity and HL, here we propose that stronger evidence would emanate from using more precise methods for evaluating both whole body and local fatness.

Though the molecular rationale has not yet been convincingly elucidated in the literature, inflammation is common to obesity and HL. In fact, the tumor microenvironment, particularly the repertoire of non-neoplastic cells and molecules produced by them, seems to exert a strong influence on tumor cell growth, evasion, survival, and diversion of immunological mechanisms. The obesity-HL association could reflect the interaction of molecules produced by adipocytes in the tumor microenvironment and the HRS cells. Some molecules, such as IL-6, IL-3, IL-7, TNF-α, YKL-40, and NF-kB and JAK/STAT pathways, seem to support this association. In a topic where the literature has not provided the luxury of clinical trials and data, the development of new molecular biomarkers based on adipokine pathways may add information as clinical outcome predictors. Their incorporation into prognostic models may improve our understanding of the biologic correlates of obesity and HL. Moreover, if demonstrated, mediators of the effect of adipocytes in the bone marrow metastatic Hodgkin lymphoma microenvironment represent an additional potential therapeutic target.

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Compliance with ethical standards

Conflicts of interest None

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