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REVIEW

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The role of trogocytosis in immune surveillance of Hodgkin lymphoma

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ABSTRACT

Hodgkin lymphoma (HL) is a unique type of hematopoietic cancer that has few tumor cells but a massive infiltration of immune cells. Findings on how the cancerous Hodgkin and Reed-Sternberg (HRS) cells survive and evade immune surveillance have facilitated the development of novel immunotherapies for HL. Trogocytosis is a fast process of intercellular transfer of membrane patches, which can significantly affect immune responses. In this review, we summarize the current knowledge of how trogocytosis contributes to the suppression of immune responses in HL. We focus on the ectopic expression of CD137 on HRS cells, the cause of its expression, and its implication on developing novel therapies for HL. Further, we review data demonstrating that similar mechanisms apply to CD30, PD-L1 and CTLA-4.

Hodgkin lymphoma

Hodgkin lymphoma (HL) affects around 80,000 people worldwide each year, accounting for around 0.4% of all cancers.[1] HL is a very common cancer in young adolescents (15–19 years old), amounting to 12% of all cancers in this age group in the United States.[2] The standard diagnosis and classification of HL are based on the morphological and immunohistochemical identification of the Hodgkin and Reed-Sternberg (HRS) cells in excisional biopsies. HRS cells are large cells that can be mononuclear or multinucleate. Classical HL (cHL) makes up over 90% of all HL cases and is the focus of this review, while the other 10% represent the nodular lymphocyte predominant type of HL. Another unique feature of HL is that HRS cells only constitute around 1% of the tumor mass whereas the majority of the tumor is made up of infiltrating immune cells.[3,4] Therefore, it is an interesting question how HRS cells evade immune surveillance in such an immune cell-rich environment. Based on current understanding, HRS cells express inhibitory ligands (e.g. PD-L1), reduce expression of immunogenic proteins (e.g. major histocompatibility complex class I (MHCI)), secrete immunosuppressive cytokines, chemokines, metabolites and extracellular vesicles to attract normal cells, and transform them into suppressive cells (e.g. regulatory T cells (Tregs) and Tumor associated macrophages (TAMs)).[5,6] Their complex interactions within the HL microenvironment have been well summarized and discussed.[5–8] This review will focus on the contribution of trogocytosis,[9,10] also called transendocytosis,[11] to the establishment of the immunosuppressive microenvironment in HL.

HL used to be a more deadly disease in previous times. Thanks to irradiation therapy and combination chemotherapy, the 5-year survival rate is currently above 90%. Nowadays, minimizing the toxicity while preserving the efficacy of the therapy is a pivotal issue of HL treatment.[12] Developing novel therapeutic approaches for refractory/relapsed HL (r/r HL) has become a focus of HL treatment since 10–20% of patients suffer from this condition.[13] Immunotherapies have changed the strategy of r/r HL treatment significantly. Brentuximab vedotin (an anti-CD30-drug conjugate) and anti-PD-1 antibodies achieve good objective response rates (>50%) in r/r HL.[12,14] Other immunotherapies, such as chimeric antigen receptor T (CAR-T) cells,[15–18] are attracting intense research interest.[19]

Trogocytosis

Trogocytosis is a fast intercellular transfer of membrane fragments along with the proteins inserted into or associated with them, which can happen within minutes. Although intercellular transfer of membranes had been observed earlier in prokaryotes, the term trogocytosis was only applied to describe these transfers in mammalian cells in 2002.[20] The proteins in the small membrane fragments pinched off from the donor cell are either displayed on the acceptor cell surface or are internalized.[9,10] Therefore, trogocytosis helps explaining why certain cell type-specific proteins are present on other cells that do not express them.[21] For example, myelin basic protein-specific T cells, after being activated by allogenic antigen presenting cells (APCs), can present myelin basic protein and conalbumin antigens to other T cells in a second co-culture, indicating the transfer of membrane patches containing specific and irrelevant peptide-MHC class II (pMHCII) from the APC to the T cells.[22] Although the transfer of proteins is not specific, trogocytosis is mediated and facilitated by specific ligand-receptor interactions. The anti-MHC antibody (OX6) could block the transfer of pMHCII in aforementioned allogenic reactions.[22] Therefore, trogocytosis mediated by specific antigen-TCR interactions can aid in the discovery of novel epitopes for clinically employed TCR.[23]

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Consequences of trogocytic transfer of membrane patches are diverse depending on the functions of proteins embedded in these membrane patches. Although trogocytosis has also been reported between many nonimmune cells and even between tumor cells,[21,24] trogocytosis has been most commonly observed among immune cells during close cell-cell contacts. This inter-cellular transfer of membrane patches and proteins contained within them, influences ongoing immune responses. During activation by APCs, ovalbumin-specific CD4^{+} helper T (Th) cells acquired pMHCI and costimulatory ligands along with pMHCII, and the ability to mimic APCs in stimulating ovalbu-min-specific CD8^{+} T cell responses.[25,26] Strikingly, mice receiving this APC-like Th cells as a vaccine, were completely protected from developing lung metastasis caused by tumor cells with this specific antigen.[25] However, trogocytosis can also suppress immune responses. During therapeutic antibody treatments for tumors, tumor cells can escape from antibody-dependent cellular phagocytosis and cytotoxicity by Fc receptor-mediated trogocy-tosis of antigen-antibody complexes.[27] HLA-G, an immunosup-pressive molecule, has been reported to be transferred among tumor cells and immune cells, leading to a suppressive tumor environment and a dampened anti-tumor immunity.[28] Therefore, the effect of trogocytosis on immune responses needs to be analyzed on a case-by-case basis.[21] Below, we will summarize recent results on the effect of trogocytosis on HL.

Ectopic CD137 expression on HRS cells induced by Epstein-Barr virus suppresses immune responses via trogocytosis

CD137 (TNFRSF9, 4–1BB, ILA) is expressed on several types of immune cells, endothelial cells and some tumor cells.[29–31] But the function of CD137 is best studied in activated T cells. The expression of CD137 on T cells is activation-dependent.[32] When crosslinked by CD137 ligand (CD137 L), CD137 trans-duces a co-stimulatory signal to T cells, polarizing T cells to Th1 and type 1 cytotoxic T cell responses,[33–35] which are pivotal for anti-tumor immunotherapy. Because of their strong costimulatory effect, agonistic antibodies for CD137, i.e. ure-lumab and utomilumab, are being developed for cancer immu-notherapy, and are currently being tested in clinical trials.[36] Moreover, the CD137 intracellular domain is incorporated as a costimulatory signaling domain in CARs.[18] CAR-T cells with the CD137 signaling domain displayed longer persistence than CD28-containing CAR-T cells in several cancers.[37] Furthermore, CD137 L expression on tumors, such as Ewing's sarcoma and B cell lymphoma, increases tumor rejection.[38,39] Therefore, the expression of CD137 for T cell activation is of great importance for tumor eradication.

To dampen anti-tumor immune responses, some tumors such as chronic lymphocytic leukemia, elevate the plasma level of soluble CD137 (sCD137) .[40,41] HL patients do not have higher plasma levels of sCD137 at diagnosis, though sCD137 slightly decreases after HL remission.[42] Instead, HL uses another strategy to suppress CD137 L-CD137 interaction between APCs and T cells, i.e. trogocytosis. CD137 is expressed by HRS cells in 86% of HL cases as demonstrated by immunohistochemistry.[30,43] Later studies found CD137 expression on HRS cells in less but still more than half of the

HL tissues (57.4%, 60% and 65%).[44–46] This ectopically expressed CD137 not only transduces an activation signal into HRS cells, but also dampens immune activation. When activated murine B and T cells interacted, a trogocytic transfer of CD137 from T to B cells and a downregulation of CD137L on B cells were observed.[47] Similarly, the ectopically expressed CD137 on HRS cell can bind CD137L and cause an internali-zation of CD137L on the HRS cells themselves as well as on surrounding APCs, resulting in decreased PBMC proliferation and IFNγ secretion[43] (Figure 1a).

It should be noted that all the available functional studies of CD137 on HRS cells are based on HRS cell lines not primary HRS cells. However, that is unavoidable since primary HRS cells are not available. Their *ex vivo* enrichment is close to impossible due to their scarcity, and because HL is generally not treated by surgery but by chemo and radiation therapy. Simultaneous staining of CD137 and CD137L in primary HL tissues to study the correlation between CD137L expression levels and the proximity to CD137^{+} HRS cells would help translating cell line results to the in vivo situation of HL.

Moreover, ectopic CD137 decreases immune activation by a cell contact-independent manner. When treated by CD137L recombinant protein, HRS cells proliferate and secrete IL-13. IL-13 is a Th2 cytokine that can inhibit Th1 responses. Indeed, the conditioned medium from a co-culture of CD137^{+} HRS cells and monocytic THP-1 cells suppresses IFNγ secretion by PBMCs in an IL-13-dependent manner[45] (Figure 1a). Supporting the findings from HRS cell lines, the immunohis-tochemical staining in primary HL tissue detected IL-13^{+} CD137^{+} HRS cells in 58% of HL cases.[45]

HRS cells are in most cases derived from B cells, which do not readily express CD137. Nevertheless, CD137 expression on B cells can be induced by B cell receptor and CD40 signaling.[48,49] Latent membrane protein 1 (LMP1) is an Epstein-Barr virus (EBV) protein that is thought to mimic CD40 signaling, and can induce NF-κB and c-Jun N-terminal kinase activation.[50–52] Interestingly, Yoshimori et al. found that EBV induces CD137 expression on T and NK cells in lympho-proliferative disorders.[53] EBV is associated with HL pathogen-esis. EBV proteins can be detected in most HL cases, especially in developing countries.[12] Finally, our group found 96% of the CD137^{+} HRS cells being positive for LMP1, and 72% LMP1^{+} HRS cells being positive for CD137,[46] and demonstrated that LMP1 can induce ectopic CD137 expression on HRS cells via the PI3K-Akt-mTOR pathway.[46,54] Recently, three groups reported that CD137 deficiencies in humans lead to impaired lymphocytic responses and EBV-induced lymphoproliferation or lymphomagenesis.[55–57] It seems that CD137 costimulation of T cells is crucial for the control of EBV, and that EBV can hijack the ectopic CD137 expression to prevent CD137 costi-mulation of T cells, and thereby evade immune rejection.[58]

HL is rich in infiltrating immune cells, with Tregs being among them. It has been reported that Tregs express CD137, and that CD137 signaling activates Tregs.[59–62] Moreover, Tregs in non-small-cell lung cancer express CD137, and high CD137 expression correlates with poor survival.[63] In HL, CD137 is expressed not only on HRS cells but also on surrounding immune cells.[43,46] It remains to be determined what these cells are, and whether Tregs in HL express CD137 and dampen
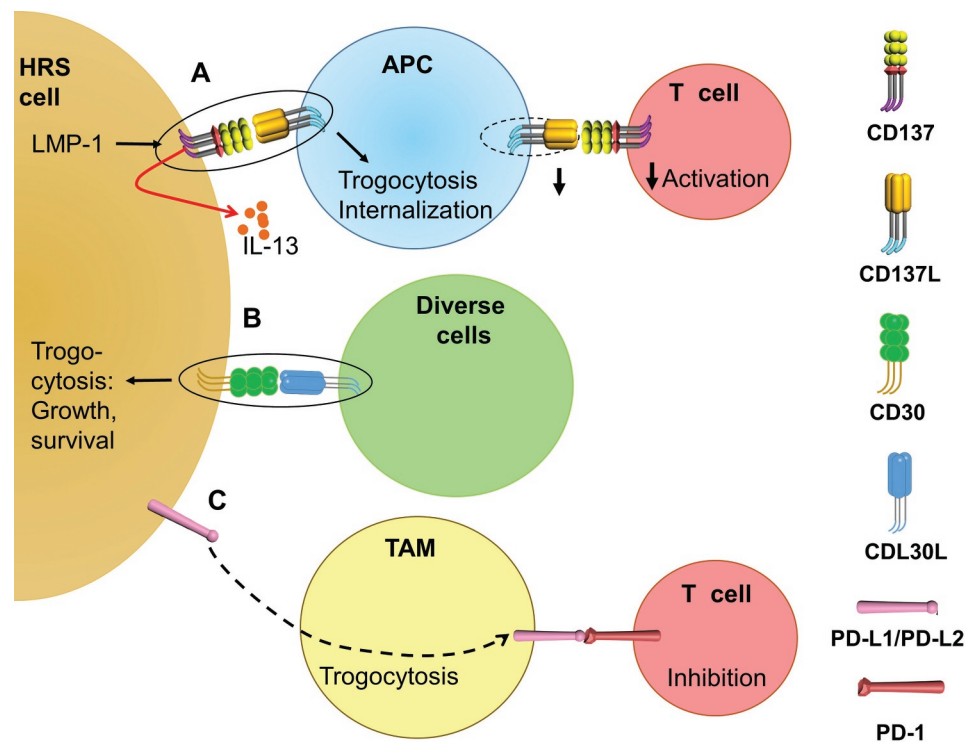
Figure 1. Trogocytosis in HL contributes to immune suppression. (a). The EBV protein LMP-1 induces the ectopic expression of CD137 on HRS cells, which can bind CD137 L and downregulate CD137 L on adjacent APCs by trogocytosis, leading to decreased costimulation of T cells. CD137 can also signal into HRS cells and induce the secretion of IL-13 that deviates the tumoricidal Th1 response away to a Th2 response. (b). CD30 on HL upon binding to CD30 L triggers a pro-growth and pro-survival signal to HRS cells, which can be enhanced by the trogocytosis of the CD30-CD30 L complex into HRS cells. (c). PD-L1 and PD-L2 on HRS cells can transfer to neighboring TAMs through trogocytosis (unknown mechanism), enhancing the T cell inhibition via PD-L1/PD-L2 – PD-1 interactions.

T cell activation by trogocytosis. Furthermore, EBV positivity is associated with a higher degree of Treg infiltration in HL.[64] It would be interesting to know if EBV can also induce CD137 expression on infiltrated Tregs in HL. In conclusion, ectopic CD137 expression on HRS cells, induced by EBV, reduces CD137L levels on APCs by trogocytosis, and signals into HRS cells leading to the secretion of IL-13, that weakens a cellular anti-HL immune responses by deviating immunity toward a Th2 response (Table 1).

Trogocytosis of CD30, PD-L1 and CTLA-4 aids HL in escaping immune surveillance

CD30 (TNFRSF8) is strongly expressed on HRS cells in cHL. The soluble form of CD30 is also highly elevated in cHL plasma, suggesting a diagnostic potential for cHL.[42] When crosslinked by CD30 ligand (CD30L), CD30 can recruit TNFR-associated factors (TRAF) and TRAF-binding proteins, leading to NF-κB and mitogen-activated protein kinase activation.[65] Although controversial results on the responsiveness of HRS cell lines to CD30 stimulation exist,[65] several groups reported the contribution of CD30 to the constitutive NF-κB activation and advantages in growth and survival for HRS cells.[66–68] Besides the conventional ligand-receptor interaction between CD30L and CD30, the CD30 L-CD30 complex can also be internalized by HRS cells via trogocytosis (Figure 1b). The internalized CD30 L-CD30 seems to be important for CD30 signaling since Latrunculin A, an actin polymerization inhibitor, significantly suppressed the calcium influx.[69]

Programmed cell death protein 1 (PD-1) is a well-established checkpoint molecule expressed on T cells. Its ligation by its

Table 1. Main findings on the induction of CD137 in HRS cells, and the role of CD137 in HL pathogenesis.

Phenomenon	Findings	References
Ectopic CD137 expression on HRS cells	57.4–86% HL tissues show CD137+ HRS cells.	Ho et al[43] Anderson et al[30] Aravinth et al[46] Rajendran et al[45] Shi et al[44]
EBV induces CD137 expression	LMP1 induces CD137 expression in HRS cell lines through Akt-mTOR pathway. 96% of CD137+ HL tissues are also positive for LMP1, and 72% of LMP1+ HL tissues are also positive for CD137.	Aravinth et al[46]
Reduced CD137 L on APCs	APCs show reduced surface CD137 L expression after coculture with CD137+ HRS cells in vitro. CD137 L – CD137 was found to be internalized and degraded in CD137 L+ cells.	Ho et al[43] Wu et al[54]
Immune modulation	Proliferation and IFNγ secretion of activated PBMCs or T cells is decreased in the presence of CD137+ HRS cell lines in a CD137 L-CD137-dependent and IL-13-dependent manner. IL-13 is coexpressed with CD137 in HRS cells in 58% of HL cases.	Ho et al[43] Rajendran et al[45]

ligands, PD-L1 and PD-L2, triggers strong inhibitory signals into T cells, inducing T cell apoptosis or anergy. PD-L1 and PD-L2 are overexpressed on HRS cells by the amplification of the 9p24.1 locus, by activator protein 1 signaling and due to EBV infection, contributing to the immunosuppressive microenvironment in HL.[70–72] Moreover, TAMs surrounding HRS cells also express high levels of PD-L1 and PD-L2.[73] The overexpression of PD-L1 and PD-L2, and the high abundance of infiltrating TAMs have been shown to correlate with a poor prognosis of HL.[72,74] Not surprisingly, anti-PD1 therapies have achieved good response rates in r/r cHL patients. PD-L1/PD-L2 expression may endow HRS cells not only to deliver inhibitory signals into T cells. Gary et al. demonstrated that PD-L1 transferred to CD8$^+$ T cells via trogocytosis is able to further crosslink PD-1, and to induce apoptosis in surrounding T cells.[75] In HL, PD-L1$^+$ HRS cells and TAMs are in close contact to T cells, which are enriched in PD-1 expression.[73] It is possible that those PD-1$^+$ T cells that are in closer contact with PD-L1$^+$ HRS cells or TAMs gain surface expression of PD-L1 by trogocytosis, and inhibit newly infiltrating PD-1$^+$ T cells or other PD1$^+$ T cells that are further away from PD-L1$^+$ HRS cells or TAMs. In support of this, more PD-L1$^+$ than PD-L1$^-$ TAMs are found in close proximity to PD-L1$^+$ HRS cells.[73] Interestingly, Kawashima et al. discovered that monocytes and TAMs in close contact with HRS cells gain PD-L1 and PD-L2 expression via trogocytosis.[76] Whether this trogocytic transfer of PD-L1 to surrounding TAMs or myeloid-derived suppressor cells also occurs in other types of tumors remains to be investigated (Figure 1c).

Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4 or CD152) is another well-known checkpoint molecule expressed on T cells, especially on Tregs. Compared to PD-1, CTLA-4 expression is more restricted to activated T cells and Tregs, and inhibits early T cell activation. CTLA-4 has a higher affinity to CD80 and CD86 than CD28 does, limiting the co-stimulatory signals T cells receive through CD28. In addition, CTLA-4 has also been shown to transendocytose CD80 and CD86, leading to CD80 and CD86 depletion on APCs.[77] Following up on the discovery of CTLA-4 transendocytosis, Gu et al. reported that induced Tregs deplete CD80 and CD86 on APCs via trogocytosis in a CTLA-4 or CD28-independent manner.[78] It would be most interesting to learn the underlying mechanism of action. It also remains to be determined if natural Tregs, especially Tregs in HL, can deplete CD80 and CD86 by trogocytosis. Clinical trials treating HL with antagonistic anti-CTLA-4 antibodies are very limited,[79,80] partially because of the more severe adverse effects compared to anti-PD-1 or anti-PD-L1 therapies. More clinical trial data will surely aid our understanding of how significant trogocytosis mediated by CTLA-4 is for maintaining the immunosuppressive microenvironment in HL.

In summary, evidence is emerging that CD30, PD-L1 and CTLA-4 are being transferred by trogocytosis, and may bestow HRS cells with growth advantages and facilitate immune evasion of HL.

Perspective

The cancerous HRS cells manipulate the surrounding immune cells and nonimmune cells to create an immunosuppressive microenvironment. Reversing this immunosuppressive microenvironment supports the eradication of HL, as exemplified by the success of anti-PD1 antibodies for the treatment of HL.[81] Trogocytosis, a common phenomenon during immune cell interactions, is hijacked by HRS cells to downregulate co-stimulatory molecules on APCs, leading to dampened anti-tumor T cell responses. Trogocytic transfer of ectopically expressed CD137 on HRS cells allows the downregulation of the immunostimulatory CD137L, and thereby helps to evade immune surveillance. The fact that CD137-deficient patients develop EBV-associated pathologies further confirms the importance of CD137-mediated T cell costimulation for immune surveillance.[55–57] Therefore, it is important that agonistic anti-CD137 antibodies used for cancer immunotherapy directly costimulate T cells via CD137, bypassing the need of interaction of T cells with CD137L on APCs. It is worth investigating whether CD137 agonistic antibodies show efficacy in curing HL, and whether they synergize with anti-PD1 or anti-PD-L1 antibodies in treating r/r HL.

Alternatively, a CD30 and CD137-bispecific antibody could be a novel therapeutic approach for HL since CD30 and CD137 are both highly expressed on HRS cells but not present on healthy cells at the same time.[83] Such a bispecific blocking antibody could not only inhibit CD30 and CD137 signaling into HRS cells, and cause antibody-dependent cellular cytotoxicity/phagocytosis (ADCC/ADCP) but also preserve CD137 L on APCs for T cell costimulation. When CD30 is targeted by brentuximab vedotin, a FDA-approved antibody-drug conjugate for cHL,[84] the transfer of CD30 to surrounding tissues by trogocytosis or extracellular vesicles may lead to an expanded CD30 sink and increased tissue damages.[85] Dual targeting of CD30 and CD137 could minimize such risks. Nevertheless, HRS cells might still evade CD30-targeting therapies by FcR-mediated extraction of antigen-antibody complexes from HRS cells via trogocytosis, leading to a reduced antigen density on HRS cells, and therefore a decreased ADCC/ADCP, as has been found for anti-CD20 therapies.[27,86,87] Orthogonal binding partners-empowered drug-free macromolecular therapeutics could be one strategy to eliminate FcR-mediated trogocytosis and at the same time induce target cell death.[88]

Besides CD137, CD40 (TNFRSF5) may also contribute to the suppressive microenvironment in HL via trogocytosis since (1) CD40-CD40 L interaction potently activates anti-tumor immune responses, (2) CD40 is highly expressed on HRS cells, and (3) trogocytosis has been reported for the CD40-CD40 L interaction during B – T cell contact.[89] Moreover, an antagonistic anti-CD40 antibody has shown modest responses in HL patients.[90] Since PD-1 and PD-L1 are a receptor/ligand pair, we expect that antagonistic anti-PD-1 antibodies will generate a similar outcome as anti-PD-L1 antibodies in terms of inhibiting trogocytosis. Nevertheless, whether the trogocytic transfer of suppressive proteins or trogocytic depletion of co-stimulatory molecules in HL can be targeted for immunotherapies, and whether they play a role in other tumors warrant more research.

Disclosure of potential conflicts of interest

The authors declare no potential conflicts of interest.

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