CD83 in Hodgkin lymphoma

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The development of combined chemotherapy with or without radiotherapy for classical Hodgkin lymphoma (HL) can be considered as a major success story in onocology. With current treatment protocols, a long-term cure is obtained in about 80-90% of patients.[1] However, these therapies come with considerable toxicity and a risk for the development of secondary cancers, which is particularly problematic not only for non-fit elderly patients, but also for young adult HL patients. Hence, there is currently much concentrated effort being put into the development of a more targeted and less toxic therapy. One very promising approach is the use of a toxin-coupled anti-CD30 antibody, brentuximab vedotin, which directly targets the Hodgkin and Reed-Sternberg (HRS) tumor cells in HL, as they consistently express high levels of CD30.[1] A second targeted therapy with exciting results from clinical studies involves antibodies against programmed cell death-1 (PD-1) or programmed cell death ligand 1 (PD-L1).[1] PD-L1 is expressed by HRS cells and inhibits PD-1-expressing activated T cells as a means of immune evasion.[2] In this issue of *Haematologica*, Li and colleagues focus on CD83 as a further potentially attractive candidate, both as a biomarker and target for therapy.[3]

CD83 is a membrane glycoprotein belonging to the immunoglobulin superfamily. It is frequently used as a general marker for dendritic cells, but it is also expressed by some other cell types, including a fraction of B cells and T cells.[4] CD83 is also released from cells, and the soluble form (sCD83) is even detectable at a low concentration in the serum of healthy individuals. This release seems to be predominantly mediated by proteolytic cleavage from membrane-anchored CD83, but may also involve differential splicing to produce a secreted form. Until recently there was no indication for the CD83 ligand(s).[5] However, a number of studies have since revealed numerous immunosuppressive functions of sCD83.[4-6]

The expression of CD83 by HRS cells was already described more than 20 years ago by Hart and colleagues.[7] A more recent study confirmed the frequent expression of CD83 by HRS cells, and showed that this can serve as a valuable marker to distinguish classical HL from anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma, which can be a difficult differential diagnosis.[8] As CD83 was initially considered to be a dendritic cell marker, its expression by HRS cells was originally interpreted as a hint for a dendritic cell origin of HRS cells,[7] but we now know that CD83 is also specifically expressed by centrocytes, the non-proliferating subset of germinal center B cells.[9] Hence, although HRS cells, which are derived from germinal center B cells,[10] have largely lost their B cell typical gene expression pattern,[11,12] expression of CD83 by HRS cells in the majority of cases of HL may reflect their germinal center B-cell origin. The retained expression of this marker by HRS cells may indicate that it is of selective advantage for HRS cells to keep it expressed and not to downregulate it;

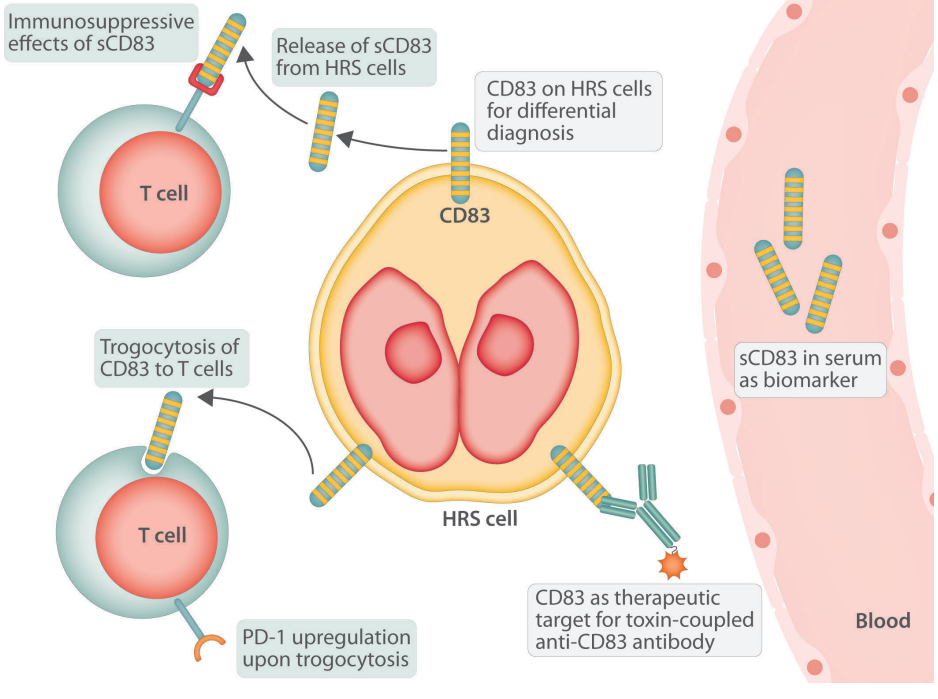

Figure 1. Features of CD83 in HL and potential clinical applications involving CD83. CD83 is expressed on HRS cells in most cases of classical HL, which can be used for differential diagnosis. Soluble CD83 (sCD83) is also released from HRS cells. sCD83 levels in serum may serve as a biomarker for disease load. sCD83 has immunosuppressive functions when binding to its still poorly characterized ligands on target cells. CD83 can also be transfered to other cells in the HL microenvironment by trogocytosis, a process in which membrane fragments are transfered from one cell to another. This process may also be immunosuppressive, as it causes upregulation of PD-1 on T cells, likely rendering them more responsive to inhibiting signals from PD-L1 on HRS cells. Finally, a toxin-coupled monoclonal antibody against human CD83 has been developed, which efficiently kills HL cell line cells. This antibody needs to be further tested for its suitability for targeted therapy. HRS: Hodgkin and Reed-Sternberg; PD-1: programmed cell death-1.

most other B-cell markers are downregulated by HRS cells.

In their study, Li and collagues studied several aspects of CD83 in HL (Figure 1).[3] First, they validated that over 80% of cases of classical HL show CD83 expression by HRS cells, and they report that in the positive cases the fraction of CD83$^+$ HRS cells varies from 10% to more than 90%. Second, they show that *in vitro*, CD83 can be transfered from HL cell line cells to T cells by trogocytosis. Trogocytosis is a process in which fragments of cell membranes are transfered from one cell to another.[13] Interestingly, the trogocytosed CD4$^+$ T cells that acquired CD83 though this process upregulated PD-1 expression, and consequently may become further suppressed in their activity against HRS cells. However, it remains unclear whether this is due to CD83 or other consequences of acquisition of membrane fragments from HRS cells. Third, extending upon an earlier observation by Hart and colleagues that a HL cell line releases sCD83,[14] the group now shows that this is also a feature of other HL cell lines, and that sCD83 contributes to the inhibition of the proliferation of stimulated T cells. This became evident from the observation that the inhibitory effect of supernatants from HL cell line cultures on T-cell proliferation was partially abolished when sCD83 in the supernatants was captured by an anti-CD83 antibody. Fourth, serum levels of sCD83, measured by the enzyme-linked immunosorbent assay (ELISA), correlated with clinical response; this, however, requires more detailed analyses, as only six patients were studied in the work by Li and colleagues. Fifth, a human anti-human anti-CD83 antibody (3C12C) was tested for its suitability to target HRS cells. Whereas the unconjugated antibody had variable cytotoxic effetcs when tested on three HL cell lines, toxicity became more pronounced and consistent when the antibody was coupled to monomethyl auristatin E (MMAE). The unconjugated form showed no general toxicity when applied to non-human primates, baboons. However, B-cell numbers where reduced in the animals, a fact from which the authors conclude that 3C12C has a targeted effect, as a fraction of B cells in baboons expresses CD83. Thus, 3C12C-MMAE should be further modified and tested as a novel targeted treatment option for HL patients.

The multifaceted study by Derek Hart and his team addresses a multitude of aspects about the biology of CD83 in HL and its clinical implications. This will, hopefully, stimulate more investigative work on this interesting topic. Regarding the application of the anti-CD83 antibody for the treatment of HL patients, a number of critical questions need to be addressed in future studies. The presence of sCD83 in HL patients may pose a major restriction for a successful therapy by capturing anti-CD83 antibodies, which may cause difficulty in obtaining high enough concentrations of free antibody in the lymph nodes to attack the HRS cells. It is a possibility that the capturing of sCD83 may be part of an efficient therapy, as sCD83 has immunosuppressive features, therefore reducing its concentration may work synergistically with the direct killing of HRS cells. A further caveat is that 3C12C-MMAE may also eliminate mature dendritic cells, which are CD83$^+$, and thereby impair normal immune responses in patients. Neverheless, positive therapeutic effects may predominate also in this regard if dendritic cells in the HL microenvironment, which are considered to contribute to the complex immune evasion strategies in HL,[2,15] are efficiently eliminated by the antibody-drug conjugate treatment. Moreover, although administration of 3C12C had no toxic effects on baboons, it remains to be clarified what the off-target toxicity of the toxin-coupled form of the antibody is, this being that which one would like to use in therapy. Finally, as most cases of HL express CD83 at levels detectable by immunohistochemistry only on a fraction of HRS cells (whereas CD30, the target of brentuximab vedotin, is expressed on virtually all HRS cells), it remains to be clarified how efficiently the HRS cell clone is eliminated when exposed to the anti-CD83 antibody toxin conjugate.

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