CD137 (TNF-receptor superfamily 9 (TNFRSF9), 4-1BB) is a member of the tumor necrosis factor (TNF) receptor family, and a potent costimulatory molecule on activated T cells and NK cells. CD137 is also a promising target for tumor immunotherapy, as CD137 signaling greatly enhances immune responses against various cancers in human and mouse.1,2 Agonistic antibodies against CD137 are being currently explored in several clinical trials for tumor immunotherapy.3 Since only T cells that are activated via the T cell receptor express CD137, and since CD137 expression is transient, CD137 marks recently antigen-specifically activated T cells, and therefore CD137 agonists allow a comparatively specific costimulation of a T cell response.4 CD137 is not only important for anti-cancer responses but also for generating effective immunity against viruses including, influenza, herpes simplex virus 1, lymphocytic choriomeningitis and vesicular stomatitis virus.5

CD137 ligand (CD137L) is expressed on antigen-presenting cells, and upon interaction with CD137L, CD137 triggers a T cell response via TNF-receptor associated factor 1 and 2 (TRAF1 and TRAF2), and activation of the transcription factor NF-κB.6 CD137 costimulation increases proliferation, the secretion of IFN-γ and the cytolytic activity of T cells. These activities reflect CD137 being a main driver of cellular, type 1 helper T cell (Th1),3 type 1 cytotoxic T cell (Tc1)-polarized immune responses.2

Finally, after 30 years of research on CD137, three recent publications characterize 6 naturally occurring mutations in 8 patients in CD137 which greatly enhance our understanding of the CD137 biology, and connect hitherto separated areas of research.

Alosaimi et al. identified a homozygous missense mutation in CD137 in two unrelated patients with recurrent infections, persistent Epstein-Barr virus (EBV) viremia, and EBV-induced lymphoproliferation. The mutation abolished surface expression of CD137 on activated T cells, resulting in a diminished proliferation, IFN-γ secretion, perforin expression and a reduced cytotoxic activity of CD8+ T cells upon stimulation with allogeneic and human leukocyte antigen (HLA)-matched EBV-transformed B cells.8 Somekh et al. analyzed four different patients with four distinct homozygous mutations in CD137 that reduced or abolished CD137 expression. Defects were seen in T cell activation and in the diversity of the TCR repertoire. For one patient, the authors proved that the mutation in CD137 was the cause of the reduced T cell proliferation capacity by a gene rescue experiment, i.e. by transducing wild type CD137 into the patient T cells which restored activation-induced T cell proliferation.9

Rodriguez et al. identified two siblings with a homozygous mutation in CD137 that prevented CD137 protein expression. Both siblings suffered from a persistent high EBV viremia, with EBV mainly being present in T cells. While the older sibling had an additional homozygous mutation in PIK3CD, a subunit of PI3K, and additional pathologies, no other mutations were found in the younger sibling, so that her pathology can be ascribed to the absence of CD137. T cells from the two siblings were unable to proliferate when cocultured with CD137L-expressing cells but upon lentiviral gene rescue of CD137 expression, CD137L-induced proliferation was restored. The authors conclude that the lack of CD137 costimulation prevented the clearance of EBV-infected T cells.10

Two of the four patients analyzed by Somekh et al. suffered from an EBV-related B cell lymphoma, Hodgkin’s lymphoma (HL) and Burkitt’s lymphoma, respectively, and one patient described by Alosaimi et al. presented with HL.8,9 One patient analyzed by Rodriguez et al. suffered from EBV-associated T cell lymphoproliferative disease, and finally succumbed to hemophagocytic lymphohistiocytosis (HLH).10 Thus, a common denominator of the three studies is that mutations in CD137 facilitate EBV-associated diseases, implying that under normal conditions CD137 limits EBV in causing pathology. This notion is supported by the diminished cytotoxic T cell response against EBV-infected B cells in the two patients analyzed by Alosaimi et al.8
The 8 patients were inflicted by infections from a range of different pathogens which varied among the patients. But the common denominator is EBV. 7 of the 8 patients suffered from EBV viremia and the 8th patient suffered from Burkitt’s lymphoma, an EBV-associated malignancy. This indicates that CD137 is essential for controlling EBV, and that the CD137-costimulated T cell response is a major reason why EBV is latent and asymptomatic in the vast majority of infected people. It can also explain the fact that EBV-associated diseases are comparatively rare, considering that 90% of the world population is infected.

CD137 is expressed by follicular dendritic cells and follicular helper T cells (Tfh) implying a function in B cell affinity maturation and development. Accordingly, all 4 patients analyzed by Somekh et al. had increased proportions of immature B cells and decreased proportions of memory B cells and plasmablasts and abnormal immunoglobulin levels. This phenotype was also observed in the two patients analyzed by Rodriguez et al., where memory B cell numbers were severely reduced. Although B cell subsets were not analyzed by Alosaimi et al., low IgG and high IgM levels, and a poor antibody response to tetanus toxoid and an absent recall response to pneumococcal polysaccharide vaccine, in one of the two patients indicate a disturbance in B cell maturation. Somekh et al. also analyzed Tfh numbers and found reduced counts in 3 of the 4 patients. These findings clearly document the importance of CD137 – CD137L interaction for the humoral immune response.

The TNF and TNF receptor families, to which CD137L and CD137 belong, contain 19 and 27 members, respectively, which can be regarded as evidence that costimulation is redundant. Redundancy is certainly the case for more general functions such as enhancement of T cell proliferation and cytokine secretion. But the phenotype of the 8 patients suggests that CD137, and possibly some other costimulatory molecules, also have non-redundant, specialized functions.

This mosaic of partial redundancy and unique functions is exemplified by CD27 and its ligand, CD70, also members of the TNFR and TNF families, respectively, which share many features with CD137 and CD137L such as T cell costimulation. But CD27 and CD70 are also essential for immunity against EBV, and homozygous mutations in them lead to EBV-associated diseases ranging from to HLH to HL. The 8 patients were inflicted by infections from a range of different pathogens which varied among the patients. But the common denominator is EBV. 7 of the 8 patients suffered from EBV viremia and the 8th patient suffered from Burkitt’s lymphoma, an EBV-associated malignancy. This indicates that CD137 is essential for controlling EBV, and that the CD137-costimulated T cell response is a major reason why EBV is latent and asymptomatic in the vast majority of infected people. It can also explain the fact that EBV-associated diseases are comparatively rare, considering that 90% of the world population is infected.

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a signal transduction of CD137L into the cells it is expressed on.\textsuperscript{29,30} This reverse CD137L signaling would also be affected in the absence of CD137. Since reverse CD137L signaling enhances APC activity, it contributes to the immune stimulation by CD137 forward signaling which costimulates T cell activity and activates NK cells.\textsuperscript{1,2} It is therefore possible that the observed phenotypes, or aspects of them, are due to a combined lack of CD137L reverse signaling and CD137 forward signaling.

The bright side of these new insights is that EBV has given away what is dangerous to it, which seems to be a CD137-costimulated immune response. On the basis of this knowledge, CD137 agonists should be explored for treatment of EBV-associated malignancies such as, NKTCL, Burkitt’s lymphoma and HL.

**Abbreviations**

EBV  Epstein-Barr virus  
HL  Hodgkin lymphoma  
HLH  Hemophagocytic lymphohistiocytosis  
HRS cells  Hodgkin and Reed-Sternberg cells

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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