Editorial

CD160: a multifunctional cell surface receptor

Volume 1 Issue 4 - 2014

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Received: September 19, 2014 | **Published:** September 20, 2014

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CD160 was identified by the monoclonal antibody BY55 as an 83-kDa molecule at the cell surface of human NK cells.[1] Initially, CD160 was recognized as an activating receptor on CD56dim NK cells where it triggers cytokine production and cytotoxicity upon engagement by MHC-I molecules on target cells.[2,3] BY55 antibody recognized a glycosylphosphatidylinositol (GPI)-linked molecule consisting of a single extracellular Ig-like domain.

More recently other isoforms were unveiled including a transmembrane (TM) form and decoy receptors lacking the Ig-like domain, essential for ligand binding. Unfortunately these isoforms were detected as alternative transcripts mRNA or by Western blot, but until now no antibody is able to recognize the native transmembrane form at the cell surface. CD160 can also be found as a soluble form in the serum and extracellular fluids. This soluble form is produced from the CD-160-GPI by a juxta-membrane enzymatic cleavage by a phospholipase-D.[4] This soluble CD160 impaired NK activation, possibly by competing for binding to MHC-I molecules. CD160 was not only found to be expressed on NK cells but it was also detected at the surface of CD8 T cells.[5,6] a minor subset of circulating CD4 T cells,[7] cutaneous T cells,[8,9] γδ T lymphocytes, intestinal intraepithelial T cells, activated endothelial cells,[10] and mast cells.[11] Of note, whereas human B cells lack CD160 expression, B-cell chronic lymphocytic leukaemia (CLL) expresses CD160 both at the protein and mRNA level.[12]

However, despite this wide CD160 expression, it seems that the trans-membrane CD160 isoform expression is restricted to the NK compartment. CD160 was also found expressed in mouse NK cells and CD8+ activated and memory T lymphocytes,[13] where, as in humans, it interacts with classical and non-classical MHC-I and CD1d.[14] Triggering CD160 at the surface of the various human cell types resulting in either cell activation or inhibition. This is particularly true for T lymphocytes where CD160-GPI was reported to either mediate co-stimulatory effect on CD8 T-cell activation upon binding to MHC-I ligands or have a co-inhibitory role on CD4 T-cell activation upon binding to herpes virus entry mediator (HVEM), an alternative ligand of CD160.[15] This opposite co-regulatory function of CD160 is intriguing but that may depend on the nature of the unknown signalling molecules to which the CD160-GPI receptor may associate with, to mediate its functions. It is clear that the molecular structure of the CD160 receptor is important for its recognition capacity.

In Western blot CD160-GPI is detected, in reducing conditions, as an 83 and a 50 kDa bands, far from the 17.5 kDa estimated from its amino-acid sequence. The same observations have been made for the CD160-TM detected as 100 kDa molecule in Western blot for an estimated molecular mass of 25.6 kDa. CD160 is therefore present at the cell surface as multimers possibly mainly a trimer and at lower frequency a dimer. This uncertainty about the true CD160 molecular complexes expressed at the lymphocyte surface needs to be clarified to understand the proper ligand binding capacity of CD160 and its function in terms of co-regulatory signals. Besides, as CD160 expression appears tightly regulated in lymphocytes, analysis of the mechanisms controlling gene expression were of interest. CD160 have been clone on human chromosome 1.[16] Analysis of its promoter region identified several conserved transcription binding sites in its minimal promoter region. Among these the AML1/RUNX1 transcriptional regulator was shown to be essential for CD160 expression.[17] RUNX family proteins play an important role in the NK cell differentiation.[18]

For example, AML-2 was identified as the predominant KIR binding factor controlling clonally expressed KIR genes during NK cell development[19] and AML-1 participates to the transcriptional control of important genes implicated in cytotoxicity such as IL2, IFN-γ and granzyme B.[20,21] Like in NK cells where CD160 is present at the surface of CD56dim, CD160 expression is fairly well associated with cytotoxic T or effector-memory lymphocytes. In the skin a resident CD4+ effector-memory T cell population, representing about 30 % of the cutaneous CD4+ T cells have been identified that express CD160 and skin addressing molecules such as CLA and CCR4.[9] These cells have a cytotoxic potential and are probably important for skin immunosurveillance but the precise regulatory role of CD160 in this context is still unknown.

On the other hand CD160 expression has been shown on growing, but not quiescent endothelial cells.[10] Here CD160 was clearly an inhibitory receptor as its cross-linking lead to an antiangiogenic effect in several model of neovascularisation.[22] This demonstrates the multifunctional effect of the amazing CD160 receptor. More studies are needed to fully understand the specificities and the functions of this receptor and its isoforms.

Acknowledgements

None.

Conflicts of Interest

There is no conflict of interest.

Funding

None.

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Citation: Schmitt C, Schmitt AMC, Giustiniani JG, et al. CD160: a multifunctional cell surface receptor. *MOJ Immunol.* 2014;1(4):11–12.
DOI: 10.15406/moji.2014.01.00021