ImmunoTools *special* Award 2013

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CEACAM expression and function in activated T- and B-cells

(Beside IL2, which cytokines are able to up-regulate the CEACAM1 expression and how does that influence the functional potential of B- and T cells)

CEA-related cell adhesion molecules (CEACAMs) are members of the carcinoembryonic antigen (CEA) gene family, which belongs to the immunoglobulin supergenfamily. In general, the highly glycosylated CEACAMs are composed of a single immunoglobulin variable (IgV)-like N-terminal (N) domain followed by zero to six Ig constant (IgC)-like domains of A and B subtypes. Due to its orthologs found in numerous species, CEACAM1 was identified as the ancestral founder molecule of the CEACAM-family. CEACAM1 mostly appears in at least two co-expressed isoforms one with a long (CEACAM1-L; 73 amino acid), one with a short (CEACAM1-S; 10 amino acid) cytoplasmic domain. The cytoplasmic domain of CEACAM1-L contains tyrosine residues within an immunoreceptor tyrosine inhibition motif (ITIM) that is crucial for signal transduction. CEACAM1 is expressed in several leukocyte-subtypes, most epithelia and endothelia of newly formed small blood vessels. The CEACAM1 expression is up-regulated in activated granulocytes, B- and T-lymphocytes as well as in confluent, contact-inhibited epithelial cells. Functionally, CEACAMs represent adhesion receptor proteins influencing pleiotropic effects. Beside mediating homophilic and heterophilic cell-cell adhesion via its N-domain, CEACAM1 controls apoptosis, cell migration, cell invasion, morphogenesis, Insulin metabolism, endocytosis, angiogenesis, lymphangiogenesis, and cell proliferation. The intercellular adhesive bond of CEACAM1 is rather weak. Thus, CEACAM1 seems to represent a sensor molecule at the cell surface that regulates cellular communications and makes cells more accessible to react to certain stimulations. Nowadays it is well described that CEACAM1 can mediates these manifold functions because it supports various well known receptors like the T and B cell receptor, VEGFR1-3, EGFR, GM-CSFR, TLR-2 and -4 as co-receptor.

The IL-2 triggered up-regulation of CEACAM1 in T cells was described long time ago. However, it appeared to us that IL-2 alone couldn’t be made responsible for this increased CEACAM1 expression because T cells need IL-2 treatment for at least four days before neo-synthesis of CEACAM1 appears. Usually one would expect an induction of the CEACAM1 expression within 6 - 18 h because that is the normal duration described for the completion of transcription and translation of neo-synthesized proteins. Therefore we hypothesize that IL-2 doesn't induce high CEACAM1 expression in T cells itself but triggers cellular reactions (cytokine

secretion, alteration of the extra- and intracellular expression profile) subsequently leading to the CEACAM1 up-regulation of after 4 - 6 days. Now we want to identify as many as possible cytokines from ImmunoTools, which are able to induce increased CEACAM1 expression in human leukocytes. Furthermore, we will analyze dose-response curves and kinetiks of these cytokine stimulations. I parallel, early (CD69) and late (CD25) activation markers as well as leukocyte subpopulation markers (CD3, CD4, CD8, CD19, CD14, CD16) and CFSE-based proliferation profiles will complete our characterization. We expect to identify a broad range of stimuli able to induce up-regulation of CEACAM1 in T cells and possibly further leukocyte subtypes within 18 - 24 h or later. Thereafter we will test if the releases of these stimuli are induced by IL-2 treatment (Sandwich-ELISA). Consequently, we will be able to generate T cells with high CEACAM1 expression suitable for studying the functional role of CEACAM1 in these activated T cells.