ImmunoTools *special* Award 2014

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The role of NMDA-receptors in lymphocyte activation

N-methyl-D-aspartate receptors (NMDARs) are the main ionotropic glutamate receptors involved in glutamatergic neurotransmission in the CNS. Their important role in neuronal synaptic transmission and plasticity, memory formation and neuronal diseases, including Alzheimer and Parkinson disease, depression and anti-NMDAR encephalitis, is well established. NMDARs consist of the obligatory NR1 subunit and two homo- or heterodimeric subunits formed by NR2A-D, NR3 or NR4. Activation of NMDARs requires the binding of glutamate or aspartate, the co-agonists glycine or D-serine and a membrane depolarization. NMDAR activity is effectively blocked by ifenprodil, a non-competitive antagonist, which binds to the NR2B subunits of NMDARs, and by the non-competitive open channel blockers MK801 and memantine. These pharmaceuticals have been shown to be neuroprotective in animal models of stroke, epilepsy and experimental autoimmune encephalomyelitis (EAE) and memantine is in clinical use to treat Alzheimer's disease.

Over the last years experimental evidence has emerged that immune cells, including DCs, release glutamate and can be regulated by glutamate found in the blood stream or peripheral organs. Furthermore, expression of NMDARs has been found for non-neuronal cells, including human and rodent T cells and thymocytes. For a beneficial therapeutic application of NMDAR antagonists it is important to know whether the drugs would influence T-cell function and, thereby, the adaptive immune response.

My studies showed that NMDAR antagonists reduce antigen-specific T-cell proliferation, chemokine-induced T-cell migration, and the cytotoxic function of $CD8^+$ T cells. This correlated with an impaired Ca^{2+}-mobilization, a reduced activation of the Erk1/2 and Akt signaling pathways and the nuclear accumulation of the transcription factor NFATc1. In the presence of the antagonists, Th1 effector cells showed a reduced secretion of IL-2 and IFN-γ, whereas Th2 cells produced more

IL-10 and IL-13, showing the drugs' strong influence on the generation of Th cell cytokine profiles. Using patch clamp analysis and NMDAR-deficient thymocytes, we also uncovered that NMDAR antagonists inhibit the conductivity of $K_v1.3$ and $K_{Ca}3.1$ potassium channels rather than inhibiting NMDARs, whose expression in T cells is elusive. Hence, NMDAR antagonists modulate multiple effector functions of T cells and act as immune suppressors, but $K_v1.3$ and $K_{Ca}3.1$ channels may be their major targets (*Kalhlfuß*, Simma* et al., MCB 2014*).

In further studies I plan to examine the effects of NMDAR antagonists on the differentiation of inflammatory Th17 and immunosuppressive iTreg cells, other immune cell populations, and the function of human T cells. The antibodies and cytokines provided by ImmunoTools would be extremely helpful to induce the differentiation of these Th cell populations and to analyze their profile by flow cytometry and therefore strongly support my studies.

ImmunoTools *special* AWARD for **Simma Narasimhulu** includes 24 reagents

FITC - conjugated anti-human CD4, CD45RA, CD62L, isotype control IgG2a,

PE - conjugated anti-human CD8,

PerCP - conjugated anti-human CD4,

APC - conjugated anti-human CD3, CD4,

FITC - conjugated anti-mouse Gr1, g/d TCR, isotype IgG2b,

PE - conjugated anti-mouse CD11b, CD62L, NK-cells, isotype control IgG2b,

APC - conjugated anti-mouse CD3e, CD62L, isotype control IgG2b,

recombinant mouse cytokines: rm IL-2, rm IL-4, rm IL-6, rm IL-7, rm IL-21, rm sCD40L

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