Cell Death Research - Translation and Clinical Perspective

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Over the past more than 20 years cell death research has made its way from the discovery of basic principles to a better understanding of diseases and lately the development of therapeutic intervention strategies based on molecules regulating the cell death machinery, in particular in cancer. As a consequence of early projects addressing growth control of malignant lymphocytes by creating monoclonal antibodies against putative growth factor receptors, we discovered a key apoptosis signaling pathway, APO-1/Fas, CD95 (Science 1989), followed by the first description of CD95-mediated apoptosis in human leukemia cells from patients with a particular form of T-cell leukemia (Lancet 1990, Blood 1992). Since then, the work of our group has been dedicated to address clinically relevant issues of cell death research, now called translational research. In particular, deregulated apoptosis in T-cells has been a focus for several years with contributions to HIV-pathology by showing deregulated CD95 ligand/receptor interaction and autocrine suicide in HIV (Nature 1995, Blood 1995). Also, the molecular basis of an autoimmune lympho-proliferative syndrome (ALPS), caused by mutations in the CD95 death receptor or the CD95 ligand similar to lpr gld mice was characterized (Science 1995). The major focus of our work has been on the involvement of cell death pathways in resistance and sensitivity of tumor cells and strategies to overcome therapy resistance. Following the first description of the impact of an intact apoptosis signaling pathway (CD95) for cancer chemotherapy (Nature Medicine 1996), we have developed strategies using apoptosis modifiers to sensitize resistant tumor cells for cell death induction either by conventional chemotherapy or by novel apoptosis-inducing ligands such as TRAIL. Thus we provided first proof of principal for IAP antagonists as novel apoptosis inducers/sensitizers in anti-cancer therapy (Nature Medicine 2002). We also provided first time evidence for the impact of intact apoptosis signaling by showing that simultaneous analysis of cytochrome c and caspase3 activation in individual leukemia cells ex vivo predict treatment response and outcome (Blood, 2006/2008). Along this line we recently identified specific survival pathways in a NOD/SCID/hu-ALL model which characterize high risk leukemia with early relapse and fatal outcome (Cancer Cell 2011). In the context of stem cell transplantation we developed strategies for selective induction of apoptosis ex vivo by using the well-established counterattack model, i.e. target cells expressing non-cleavable CD95 on the surface. Here, we discovered a novel function of CD95: silencing of T-cell activation by direct inhibition of T-cell receptor signaling in addition to apoptosis induction (JEM 2009). Taken together, based on our work and that of many groups, molecular insights into apoptosis regulation led to a better understanding of therapy response in conventional treatment, directed molecule-based rational treatment strategies and provided novel targets for therapeutic intervention.