

## Cell death and inflammation in cancer and beyond

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Since the beginning of research into tumor necrosis factor (TNF), the death ligand members of the TNF cytokine superfamily have been particularly attractive as potential novel cancer therapeutics because of their capacity to directly induce cell death. Soon after TNF was cloned it became clear, however, that recombinant TNF could not be used to treat cancer systemically as it was found to exert lethal inflammation when applied systemically. The same held true for the second death ligand to be identified, Fas ligand (FasL). Yet, for the third death ligand to be discovered, the TNF-related apoptosis-inducing ligand (TRAIL), this was different as TRAIL was capable of selectively inducing apoptosis in cancer cells, yet not in any essential normal cells *in vitro* and *in vivo*. However, in contrast to many cancer cell lines most primary cancer cells turned out to be TRAIL-resistant so that the field turned to identifying drugs that synergize with TRAIL in killing cancer cells. A few years ago, we discovered that combining TRAIL with CDK9 inhibition overcomes TRAIL apoptosis resistance in a panel of lung tumor cells and that it did so to a degree we had not previously achieved with any other TRAIL-comprising combination treatment. We recently showed that this combination is capable of killing cells derived from a broad range of cancers, importantly including cancers resistant to chemo- and/or targeted therapies. Our most recent results on the possible use of TRAIL as a cancer therapeutic but also on our understanding of the tumor biology of TRAIL will be presented. As TNF had been found to be a crucial player in cancer-related inflammation, in a parallel line of research we set out to better understand the biochemistry of TNF signaling and its (patho-)physiological consequences. This resulted in the discovery of linear ubiquitination as a crucial regulator of the balance between cell death and inflammation in TNF signaling. Importantly, however, it also led us to discover that the induction of cell death by TNF, rather than only TNF-induced gene activation – which was the paradigm at the time –, can induce chronic inflammation and, consequently, cause autoimmune disease. More recently we were able to show that the concept of cell death-induced inflammation expands to cell death inducers beyond TNF, including to TRAIL and FasL. Our most recent research on cell death-induced inflammation in disease will also be presented.