Summary

Comparison of immunomodulatory properties of cystatins in free-living and parasitic nematodes

Parasitic nematodes modulate the immune systems of their hosts to exploit them as long as possible. In an effort to understand the molecular mechanisms involved in this immunomodulation, I examined the role of nematode-encoded secreted protease inhibitors (cystatins). Cysele1 and Cysele2, cystatins of the free-living, non-parasitic nematode *Caenorhabditis elegans* were cloned, expressed and investigated for their impact on mice and human cellular immune responses. For comparision, previously described recombinant cystatins of parasitic nematodes were used: Av17 (Hartmann et al., 1997), a cystatin of the rodent filarial pathogen *Acanthocheilonema viteae*; and Ov17 (Schönemeyer et al., 2001), a cystatin of the human filarial pathogen *Onchocerca volvulus*.

The most striking difference in the effect of the cystatins was the impact on the proliferation of T lymphocytes. Filarial cystatins strongly suppressed the proliferation of polyclonally and antigen specific stimulated murine spleen cells and human PBMC. In contrast, the *C. elegans* cystatins had little or no effect on either type of proliferation. Different processes were investigated to find the basis for these differences. Human cathepsins involved in antigen processing and presentation by APC were differentially inhibited by the cystatins examined (mostly cathepsin S and B). Mutations in the domain of inhibition of the proteins are probably responsible. The pattern of cytokine production by polyclonally stimulated human PBMC and therefore the regulation of the immune response were differentially effected by filarial and *C. elegans* cystatins. Filarial cystatin induced the production of the antiinflammatory cytokine IL-10 whereas *C. elegans* cystatins induced the production of the proinflammatory cytokines IFN-γ and IL-12. The production of NO by murine peritoneal macrophages was stimulated by both the filarial and *C. elegans* cystatins.

My data show, that certain immunomodulatory effects of filarial cystatins are clearly different from the effects of the *C. elegans* cystatins. We propose that during evolution of filarial parasites selection for modifications in proteins pre-existing in free-living nematodes occured which targeted the immune response of their hosts resulting in reduced immune clearance.