Abstract 41:

Role of soluble and transmembrane TNFα during inflammation: focus on macrophage activation

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Usually inflammation provides host defence against infections and supports wound healing, but inflammation can also become chronic, causing several disorders in humans and animals. Tumor necrosis factor-alpha (TNFα) is a multifunctional mediator that can be expressed in a soluble (s) or transmembrane (tm) form. While sTNFα is generally associated with inflammation, the role of tmTNFα is not well understood. Yet, both sTNFα and tmTNFα are required for a fully functional immune response and both can bind to the same two TNFα receptors. Fundamental questions remain about the relative contribution of sTNFα and tmTNFα to inflammation and through which receptors they exert their activities. We aim to dissect the function of sTNFα and tmTNFα *in vivo*, during inflammation induced by injury or infections in zebrafish, with a special focus on macrophage activation. The zebrafish has several specific advantages, including: 1) transparency of embryos that allow live, non-invasive imaging of (immune) cells in real-time, 2) availability of transgenic lines expressing fluorescent proteins under the control of macrophages-, or TNFα-specific promotors, 3) availability of a well-annotated genome for gene manipulation. All this will enable us to generate new transgenic zebrafish only expressing sTnfα or tmTnfα and use Tnfα knockout lines. In a similar manner, also the expression of both Tnfα receptors can be manipulated. Altogether, this project will address fundamental questions about the relative contribution of sTNFα and tmTNFα to inflammation, with a special focus on macrophage activation and the receptors through which sTNFα and tmTNFα exert their activities.