Prospective studies on the complete dynamics of TGF-β1 latent protein dissociation

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Transforming growth factor beta 1 (TGFβ-1) is a homodimeric cytokine that influences various signal transduction pathways controlling tissue development, angiogenesis, wound healing, and hematopoiesis. Newly synthesized TGFβ-1 is complexed with a large prodomain called the latency associated peptide (LAP) that renders TGFβ-1 inactive. This restricts it from binding to its cognate receptors and activating signaling cascades. Recent studies suggest that secreted TGFβ-1 is activated through a coordinated force from integrin binding and cell contraction that mechanically unfolds LAP, subsequently releasing the activated TGFβ-1 dimer. Dysfunction of this process and overabundance of free TGFβ-1 is associated with tumorigenesis and inflammation.

The mechanical unfolding is a dynamic and large scale process. Studies show that in addition to the mechanical unfolding of LAP, release of TGFβ-1 can be induced by reactive oxygen species (ROS). We intend to image this process using complementary structural techniques. The initial steps will use x-ray irradiation and chemical methods to provide the ROS activation and x-ray free electron laser (XFEL) crystallography to reveal the initial and rapid changes on the residue level. Solution techniques will follow the rest of the process with our aim to develop fast SAXS/WAXS methods to reveal gross changes at a high degree of structural detail. The results from experimental studies will be used for computational modeling of the process. Conclusions from this work will contribute to our understanding of TGFβ-1 release and activation, which will provide insights for the development of novel therapeutics.