Protein-disulfide isomerase: the decisive off-switch of a disintegrin and metalloprotease-17

Beside their classical function in facilitating protein folding in the endoplasmic reticulum (ER) protein-disulfide isomerases (PDIs) act at the cell surface; thereby regulating various biological processes, like cell-cell adhesion or enzymatic activity. One prominent substrate of the PDI is the transmembrane metalloprotease A Disintegrin And Metalloprotease-17 (ADAM17). Besides its essential role in development, ADAM17 is involved in regeneration processes and immune defense in the adult organism. Hence, an uncontrolled enzymatic activity of the protease is associated with pathophysiological situations, like tumor progression and chronic inflammation, e.g. by the release of growth-factors and pro-inflammatory cytokines from the cell surface. Consequently, the enzymatic activity of ADAM17 has to be tightly regulated. PDI oxidoreductases act as an off-switch of active ADAM17. The detailed consequence of the PDI action on ADAM17 is described at a structural level. A drastic change within the membrane-proximal domain (MPD) of ADAM17 due to a specific disulfide-bond isomerization abrogates ADAM17 activity. However, nothing is known about the regulatory mechanisms underlying this important thiol switch. This application aims to analyze how PDI traffics to cell compartments beyond the ER. Furthermore, we will search for an enzyme with opposite activity of PDI, which mediates an on-switch of ADAM17, allowing a rapid modulation of its enzymatic activity.