Biology of the thioredoxin TXNDC15

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Immune cell function critically depends on store-operated Ca2+-entry (SOCE). The ORAI and STIM dependent activation of immune cells can also lead to local production of intracellular reactive oxygen species (ROS), the physiological function of which is not well understood. A previous screen identified four potential SOCE regulators, all belonging to the family of thioredoxins.

Thioredoxins are oxidoreductases involved in a variety of cellular processes such as catalyzing the formation of disulfide bonds with the endoplasmic reticulum, protecting proteins from oxidative aggregation, helping cells cope with oxidative stress, regulating cell death, acting as growth factors,among others. For each of these functions, subsets of specialized thioredoxins are likely responsible. Common to all thioredoxins is a TRX-Fold with at least one redox active CXX[C/S]-motif. We focused our work on one of the least studied members of human thioredoxin family, TXNDC15 (Thioredoxin-Domain-Containing-Protein 15). TXNDC15 is a predicted type 1 transmembrane protein with unknown subcellular localization and function. Many other members of the thioredoxin family are found in the ER, mitochondria, nucleus and cytosol. We set out to identify the subcellular localization and function of TXNDC15 on SOCE and to characterize its functional domains. The localization and the (mis)function of TXNDC15 is strongly affected by the type and location of the tag within the protein. A C-terminally tagged protein is retained within the ER and leads to a strong decrease in SOCE. However, placing the tag at a different location, this effect on SOCE is annihilated and localization is now mostly not within the ER but rather TXNDC15 now localizes to the Golgi apparatus, cell surface and lysosomes. Future experiments are aimed at understanding its physiological function and on identifying its interaction partners.