The role of TMX oxidoreductases in melanoma growth and invasion

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Calcium and redox signals are essential regulators of melanoma pathobiology[1]. However, information regarding molecular players involved is scarce. Here we examined the role of endoplasmic reticulum (ER)-based protein disulfide isomerases (PDI) family members thioredoxin-related transmembrane proteins 1 and 3 (TMX1, TMX3) in melanoma. Our results show that TMX1 and TMX3 are upregulated in human melanoma samples. TMX1 downregulation inhibited melanoma cell proliferation and migration *in vitro* and tumor growth *in vivo*. Moreover, TMX1-silencing led to inhibition of NFAT1 nuclear translocation, a transcription factor present in melanoma but absent in healthy melanocytes. TMX1-silenced melanoma cells displayed an enhanced mitochondrial calcium uptake and subsequent increase in intracellular H2O2 levels which were responsible for NFAT1 inhibition via oxidation of calcineurin. Antioxidant treatment reversed the TMX1-induced NFAT1 inhibition. Electron microscopy of TMX1-silenced cells depicted an altered mitochondrial morphology and distances between mitochondria and ER and plasma membrane and thereby provided evidence regarding the molecular mechanism leading to TMX1-induced inhibition of NFAT1 activity and thus melanoma growth and invasion. In summary, our study identified a novel TMX1-NFAT1 signaling axis that regulates melanoma pathobiology in a calcium and redox dependent manner. TMX1 and NFAT1 represent potential novel therapeutic targets as well as biomarkers of aggressive melanoma disease.

[1] Hanahan D and Weinberg RA, Cell, 10.1016 (2011).