PROJECT 2 (optional)

DoS: Roberto Sitia

Title: Transmission of redox signals across compartments

Curriculum: BAIO

Link to OSR/UniSR personal page:

Project description

Over 57,000 papers appear in PubMed upon entering 'antioxidant and cancer'. So far, however, trials with antioxidants have not met the expectations. H_2O_2 -the most important reactive oxygen species in human pathophysiology- is a key second messenger at low levels, but highly cytotoxic at high levels. Tumor cells are the paradigm of this duality. Their proliferation is promoted by H_2O_2 via amplification of growth factor receptor-dependent responses (Bertolotti et al., 2016). Non-lethal oxidative stress favors genome instability allowing the development of more aggressive clones. At the same time, radio- and chemo- therapy rely largely on oxidation-induced cell death. Therefore, the mechanisms that control H_2O_2 generation, diffusion and clearance are of paramount interest in oncology. It is now clear that a subset of aquaporins (AQP3, AQP8. AQP9, AQP11, Bestetti et al., 2020) are needed for efficient H_2O_2transport across membranes. Importantly, AQP8 conductivity is regulated by persulfidation of a conserved cysteine (Bestetti et al., 2018). Its gating is induced by different cell stresses, attenuating growth and facilitating drug/ radiation-induced apoptosis. AQP8 mutants unable to be regulated improve cancer cell survival and proliferation.

We now aim at understanding how cells restore AQP8 conductivity or bypass regulation, issues of particular relevance for tumor progression. During stress recovery, H_2O_2 transport is restored in about 3 hours, without requirement for protein synthesis. Our preliminary data point at a synergy between endosomal recycling and exposure to H_2S released by cystathionine gamma-lyase, an enzyme of the trans-sulphuration pathway. A series of experiments is planned to dissect the mechanisms that allow cells to regulate the gating and reopening of AQP8 and other peroxiporins. H_2O_2 fluxes, cell proliferation, migration and drug sensitivity will be analyzed upon deletion and reconstitution experiments. Regulatory molecules will be searched and identified by coprecipitation and proteomic assays available in the lab.

These experiments will help designing a better cartography of redox signaling in living cells. Considering their diverse subcellular localization and regulation, peroxiporins could be key targets in cancer pathobiology.

Skills to be acquired by the student:

Main techniques in molecular cell biology, differential proteomics and imaging.

Scientific reasoning and experimental planning.

Collecting, interpreting, discussing and summarizing data into a scientific paper and a thesis that can be defended with success.

References (max. 3)

Bertolotti M, Farinelli G, Galli M, Aiuti A, Sitia R. AQP8 transports NOX2-generated H2O2 across the plasma membrane to promote signaling in B cells. ***J Leukoc Biol.*** 2016 100:1071-1079.

Bestetti S, Medraño-Fernandez I, Galli M, Ghitti M, Bienert GP, Musco G, Orsi A, Rubartelli A, Sitia R. A persulfidation-based mechanism controls aquaporin-8 conductance. ***Science Adv***. 2018 May 2;4(5):eaar5770.

Bestetti S, Galli M, Sorrentino I, Pinton P, Rimessi A, Sitia R, Medraño-Fernandez I. Human aquaporin-11 guarantees efficient transport of H_2O_2 across the endoplasmic reticulum membrane. ***Redox Biol.*** 2020 28:101326.