Calcium dyshomeostasis as a marker of ER stress, chemotherapeutic drug resistance and neurodegeneration

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- Dysregulation of calcium signaling is emerging as a key feature in the pathogenesis of cancer and of neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease (PD), and Huntington’s disease (HD), and targeting this process may be therapeutically beneficial. Under this perspective, it is important to study proteins that regulate calcium homeostasis in the cell.

- Sorcin is one of the most expressed calcium-binding proteins in the human brain. Its overexpression increases endoplasmic reticulum (ER) calcium concentration and decreases ER stress in the heart and in other cellular types. Sorcin may counteract the increased cytosolic calcium levels associated with neurodegeneration. We demonstrated that Sorcin regulates ER calcium transients: Sorcin increases the velocity of ER calcium uptake (increasing SERCA activity), decreases calcium efflux from ER (downregulating RyR) and increases calcium exchange by regulating NCX. We recently showed that Sorcin expression levels are strongly increased in cellular, animal, and human models of AD, PD, and HD, vs. normal cells. Sorcin partially colocalizes with RyRs in neurons and microglia cells; functional experiments with microsomes containing high amounts of RyR2 and RyR3, respectively, showed that Sorcin is able to regulate these ER calcium channels. The molecular basis of the interaction of Sorcin with RyR2 and RyR3 was demonstrated by SPR. Sorcin also interacts with other ER proteins as SERCA2 and Sigma-1 receptor in a calcium-dependent fashion. We demonstrated that Sorcin may represent both a novel early marker of neurodegenerative diseases and a response to ER and cellular stress dependent on neurodegeneration.

- Calcium dyshomeostasis is the cause of hypercalcemia of malignancy. Bisphosphonates, a group of molecules that reduce plasma calcium by inhibiting bone resorption, are used to regularize blood calcium disturbances. Sorcin is overexpressed in cancer cells, in particular in drug-resistant cancer cells, where it is co-expressed with the ABCB1 and ABCB4 efflux pumps, and plays an important role in calcium dyshomeostasis and in multidrug resistance (MDR) in tumors, since its expression confers resistance to doxorubicin and to other chemotherapeutic drugs. We demonstrated that Sorcin is able to bind doxorubicin, vincristine, paclitaxel and cisplatin directly and with high affinity. Sorcin limits the toxic effects of the doxorubicin in the cell; Sorcin silencing increases cell death upon treatment with doxorubicin, increases the accumulation of chemotherapeutic drug in cell nucleus, decreases the expression of ABCB1 and doxorubicin efflux via ABCB1.

References:

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