

New strategies focused on endoplasmic reticulum for treatment of human diseases

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Accumulating evidence suggests that many serious human diseases related to oxidative stress (diabetes, cancer, heart and neurodegenerative diseases) are associated with stress of endoplasmic reticulum (ER) and are called also ER diseases. Proper function of ER requires a steep calcium gradient. In the extracellular space, the Ca^{2+} level reaches 1 mM, whereas in the intracellular space it is maintained around the value of 100 nM [1]. Without this gradient cells undergo ER stress and cell death. ER is a network of membranes with mutual functions, focused on production, processing, and transport of proteins and lipids as well as on maintaining the calcium storage. Moreover, ER possesses regulatory abilities like redox controlling, cell signaling and cell death. To summarize these properties, ER is deciding about survival or death of cells.

A novel therapeutic approach is to develop drugs targeted to ER dysfunction. ER homeostasis, i.e. normal function of ER, is maintained by calcium and redox homeostasis as well as by correct protein folding. Sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) is an enzyme playing a crucial role in maintaining a physiological level of Ca^{2+} inside the cells.

In addition to the SERCA, the calcium channels such as ryanodine receptors and inositol trisphosphate receptors are another possibilities as targets to influence ER calcium homeostasis [2].

Both physiological and pathophysiological levels of ROS/RNS regulate cell functions by modifications of SERCA. This regulation of cell function may suggest new strategies to prevent vascular diseases and development of cancer. Flavonoids and other small molecules are able to elevate cytosolic (Ca^{2+}) at least partially via SERCA and thus may be a useful tool for preventing cancer development. On the other hand, some flavonoids significantly increased cell viability and protected against cardiomyocyte apoptosis *via* preservation of SERCA function, which can be a novel strategy against cardiovascular diseases associated with oxidative stress [3,4]. ER plays also a more important role in type 2 diabetes and its complications than believed previously. Pancreatic

beta cells and neurons are particularly sensitive to ER dysfunction associated with impairment of calcium homeostasis.

Recently we found a correlation between decrease of SERCA activity induced by the quercetin derivative chloronaphthochinonequercetin and its anticancer effect in colorectal cell lines HCT-116 and HT-29 [5]. Relationship between SERCA activity decrease and apoptosis was indicated also with respect to curcumin [6]. On the other hand, tetra(trimethylgalloyl)oxyferuloylquercetin, a derivative which increased SERCA activity, showed protective effect on pancreatic beta cells [7].

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