

Roles for Flavonoid Apigenin in Regulation of the Mammalian Stress Response

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Abstract

Upon accumulation of unfolded proteins in the endoplasmic reticulum (ER), cells activate an intracellular signal transduction program called the Unfolded Protein Response (UPR). In mammalian cells, the UPR is an adaptive response for survival, and it is initiated by activation of three sensor proteins - PERK, ATF6 and IRE1- located in the ER membrane. The UPR increases folding capacity of the ER by up-regulating ER molecular chaperones and folding enzymes.

Here we demonstrate that flavonoids, plant pigments ubiquitous to green plant cells, affect the mammalian UPR. We created an UPR reporter vector in which translation of enhanced green fluorescence protein (EGFP) requires IRE1-dependent splicing of the XBP1 intron. Using Chinese Hamster Ovary (CHO) cell lines that express the UPR reporter and wild-type CHO cell lines we show that flavonoid apigenin reduces the ER stress response: expression of CHOP and ER chaperone GRP94 was reduced by apigenin treatment. However, apigenin pretreatment was not sufficient to suppress thapsigargin or tunicamycin-induced ER stress response. In addition, apigenin treatment was not enough to induce IRE1-dependent splicing of the XBP1 intron. The results suggest a possibility that apigenin reduces ER stress response by inhibiting PERK or ATF6 pathway.

References

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