Metformin induces ER stress-dependent apoptosis through miR-708-5p/NNAT pathway in prostate cancer.

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Abstract

Although the antitumor role of metformin has been widely reported, the molecular mechanism of this biguanide agent in the inhibition of tumor progression remains unclear. Here, we identified miR-708-5p as a novel target of metformin in prostate cancer cells. Metformin promotes increased expression of miR-708-5p, leading to suppression of endoplasmic reticulum (ER) membrane protein neuronatin (NNAT) expression and subsequently induces apoptosis of prostate cancer cells through the ER stress pathway. Further, miR-708-5p-induced knockdown of NNAT is associated with downregulated intracellular calcium levels and induced malformation of ER-ribosome structure revealed by electronic microscopy. Meanwhile, the unfolded protein response regulator CHOP, p-eIF2α, calreticulin, GRP78 and ATP2A1, all of which are also considered as ER stress markers, are upregulated by metformin and miR-708-5p. Taken together, our findings clearly demonstrate that metformin stimulates increased expression of miR-708-5p to target the NNAT-mediated response to ER stress and apoptosis. This novel regulatory mechanism of metformin in prostate cancer cells not only advances our knowledge on the molecular mechanism of metformin but also provides a promising therapeutic strategy by targeting miR-708-5p and NNAT for prostate cancer treatment.

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