ENDOPLASMIC RETICULUM STRESS AS A TOOL TO INFLUENCE PROTEIN ARGININE METHYLTRANSFERASES IN PRIMARY CLEAR CELL RENAL CARCINOMAS AND NONTRANSFORMED RENAL CELLS

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Protein arginine methyltransferases (PRMTs) are responsible for the methylation of arginine side chains of histones and nonhistone proteins. Dysregulation of these transferases has been linked to tumorigenesis, with possible involvement of modulation of the activity and function of a number of endoplasmic reticulum (ER) stress-associated proteins. We aimed to elucidate the role of PRMTs and the link between UPR activity and the expression of individual PRMTs and to determine whether ER stress in primary clear cell renal cell carcinoma (CCRC) cells and healthy renal cortex cells leads to changes in the expression of PRMTs. For these experiments, we used primary cells isolated from resected CCRC and associated healthy renal cortex tissue. Cells were cultured as adherent 2D cultures and 3D tubuloids. We found that although high concentrations of tunicamycin were cytostatic, lower concentrations stimulated proliferation. Tunicamycin did not affect CCRC cell viability unless used at very high concentrations but induced ER stress (quantified as an increase in BiP expression). We found different amounts of transcripts of some PRMTs in CCRC cells compared to healthy renal cortex cells. We showed that the transcription rates of genes for PRMTs varied depending on the culture method, with PRMT6, 7, and 9 transcription rates being several-fold higher in cells cultured as tubuloids. We found interindividual differences in the transcription rates of PRMTs in cells exposed separately to tunicamycin and TUDCA. We measured a significant increase in the transcription rate of some PRMTs after treatment of CCRC cells from patient 77 with tunicamycin and TUDCA, and the same effect of this condition was observed in healthy renal cortex cells from the same patient. A similar effect of the condition with both agents was also measured in healthy renal cortex cells of patient 57, and the affected PRMTs differed depending on the culture method. Based on the results, affecting the activity and/or expression of PRMTs can be considered a legitimate means of influencing the consequences of ER stress in both CCRC cells and healthy renal cortex cells. Follow-up experiments will focus on detecting biomolecular condensates typical of increased PRMTs` activity.

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