Analysis of the unfolded protein response regulation by the mono-ADP-ribosyltransferase PARP16 in a cellular model of osteosarcoma

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The mechanisms underlying the post-translational regulation of eukaryotic unfolded protein response (UPR) represent an important aspect in cell biology. The mono-ADP-ribosylation of two key UPR regulators, PERK and IRE1α, by the endoplasmic reticulum (ER) mono-ADP-ribosyltransferase PARP16 represents a critical step for the full activation of the UPR upon ER-stress. Ineffective UPR response can represent, in certain cases, a deleterious scenario for the survival of tumor cells subjected to ER-stress conditions.
We investigated the regulation of UPR upon PARP16 depletion in a cell model of osteosarcoma, a tumor in which pharmacological treatment is limited by post-therapy drug-resistance. Using gene silencing and genome editing approaches we tested the potential of PARP16 as target for the treatment of this tumor. Our analyses showed that upon ER-stress, depletion of PARP16 in U-2 OS cells by siRNA caused an altered phosphorylation of eIF2a (p-Ser51), the major substrate of the UPR-regulating kinase PERK. In the same conditions, we observed the proteolytic cleavage of PARP1 in both U-2 OS and cell lines from different tumors, confirming that PARP16 is involved in cell survival. To further characterize this aspect, we generated a PARP16^{KO} U-2 OS cell line and tested its sensitivity to ER-stress. From our results, it emerged that the pharmacological treatment with ER-stress inducers, caused a larger inhibition in the proliferation of PARP16^{KO} cells compared to control cells.
Overall, the results obtained suggest that interfering with the function of PARP16 could have a potential impact on improving the treatment of osteosarcoma. These observations open the possibility to test therapeutic approaches and/or molecules that aim to inhibit the function of PARP16 in tumors with low UPR in combination with ER stress inducers and in tumors that exploit high UPR to survive with the aim of increasing its sensitivity to ER-stress, favoring the activation of cell death mechanisms.