

PERK-MEDIATED UNFOLDED PROTEIN RESPONSE ACTIVATION AND OXIDATIVE STRESS IN PARK20 FIBROBLASTS

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PARK20, an early onset autosomal recessive parkinsonism is due to mutations in the phosphatidylinositol-phosphatase Synaptojanin 1 (Synj1).

We have recently shown that the early endosomal compartments are profoundly altered in PARK20 fibroblasts as well as the endosomal trafficking. Here, we report that PARK20 fibroblasts also display a drastic alteration of the architecture and function of the early secretory compartments. Our results show that the exit machinery from the Endoplasmic Reticulum (ER) and the ER-to-Golgi trafficking are markedly compromised in patient cells. As a consequence, PARK20 fibroblasts accumulate large amounts of cargo proteins within the ER, leading to the induction of ER stress. Interestingly, this stressful state is coupled to the activation of the PERK/eIF2 α /ATF4/CHOP pathway of the Unfolded Protein Response (UPR). In addition, PARK20 fibroblasts reveal upregulation of oxidative stress markers and total ROS production with concomitant alteration of the morphology of the mitochondrial network. Interestingly, treatment of PARK20 cells with GSK2606414 (GSK), a specific inhibitor of PERK activity, restores the level of ROS, signalling a direct correlation between ER stress and the induction of oxidative stress in the PARK20 cells.

All together, these findings suggest that dysfunction of early secretory pathway might contribute to the pathogenesis of the disease.