Modulating Iron Homeostasis, Autophagy and Oxidative Stress Pathways in BPAN-derived fibroblasts: Active Compounds for Potential Therapy

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Beta-Propeller Protein-Associated Neurodegeneration (BPAN) is a rare neurodegenerative disorder caused by mutations in the WDR45 gene, which plays a critical role in autophagy. Patients with BPAN experience progressive cognitive decline, motor dysfunction, and iron accumulation in the brain, leading to increased oxidative stress and cellular damage. Dysregulation of autophagy, impaired iron homeostasis, and elevated oxidative stress are key pathological features of BPAN, making these cellular processes potential therapeutic targets. Current research focuses on identifying bioactive compounds that can modulate these pathways, offering hope for treatments that could slow or alleviate the progression of BPAN.

Our study evaluates the impact of several known and novel bioactive compounds, including NRF2 inducers, senotherapeutics, autophagy and proteasome inducers on iron homeostasis, autophagy markers, and oxidative stress response proteins in fibroblasts derived from BPAN patients. When comparing BPAN fibroblasts to healthy controls, significantly higher total iron levels were observed, particularly in older patients. Additionally, changes in autophagy proteins, oxidative stress-related cytoprotective proteins, and LAMP1 were detected, with no alterations in ER stress protein markers. Notably, evaluating expression levels of proteins related to iron homeostasis, such as ferritin, ferroportin and transferin receptor revealed that ferritin levels were markedly reduced in these BPAN-derived fibroblast.

By treating BPAN fibroblasts with various compounds at different concentrations, several active compounds were identified that significantly reduced total iron levels, bringing them close to control levels. Further evaluation of these active compounds revealed that they also enhanced expressions of autophagic markers, such as LC3 and p62, indicating enhanced autophagy flux in BPAN fibroblasts. Additionally, oxidative stress markers, including NRF2 and HO-1, were upregulated after treatment, suggesting activation of the antioxidant response. Importantly, the active compounds also positively affected ferritin levels, contributing to improved iron homeostasis in BPAN fibroblasts.

Overall, the bioactive compounds identified in our screening effectively modulated key processes involved in BPAN pathology, including iron metabolism, autophagy, and oxidative stress, , highlighting their potential therapeutic effects in addressing the dysregulation observed in BPAN cells.