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81. CHOLESTEROL METABOLISM IMPAIRMENT: A BIOMARKER OF NEURODEGENERATION?

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We have previously established an *in vivo* iron overload model using C57BL/6 mice characterized by movement disorders similar to Parkinson's disease phenotype. Midbrain analysis of iron-treated mice showed increased gliosis along with the loss of tyrosine hydroxylase labeling and the presence of ferroptosis markers. Associated with dopaminergic neuronal loss, we found cholesterol (Chol) accumulation in the midbrain ($p<0.05$). Free Chol increase was accompanied by the upregulation of SREBP1 and SREBP2 ($p<0.001$) transcription factors. To further investigate the link between Chol and ferroptosis, we used single-cell cultures of neurons, astrocytes, microglia, and primary glial cultures exposed to iron overload. Dopaminergic neurons (N27), astrocytes (C6), and mouse primary glial cultures showed increased Chol levels in intracellular compartments as well as in their secretomes after iron treatment ($p<0.001$). This rise coincided with the upregulation of genes associated with Chol *de novo* synthesis and transport, HMGCR and ABCA1 ($p<0.001$). In addition, neurons incubated with astrocytes' secretome enhanced even more their Chol content, probably due to the upregulation of the ABCA1 transporter. To study the link between Chol accumulation and ferroptosis, cells were exposed to the inhibitor ferrostatin-1. We found that ferrostatin-1 reduced Chol levels when cells were exposed to iron overload ($p<0.001$). Our findings indicate that altered Chol metabolism could be a biomarker of midbrain neurodegeneration triggered by ferroptosis, with motor impairment as an outcome.