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Et al.

Reprogramming of mTOR Signaling by Perinatal Exposure to Brominated Flame Retardant

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Mammalian target of rapamycin (mTOR), also known as mechanistic target of rapamycin, is a known metabolic master-switch. In conditions of starvation, mTOR suppresses biosynthetic programs and increases the recycling of proteins and organelles. Upon stimulation by nutrients and growth factors, however, mTOR causes activation of biosynthesis and suppression of autophagy. The mTOR-centered molecular pathway is a major pathway of growth regulation and metabolism, linked to aging and the development of cancer, obesity, type 2 diabetes, neurodevelopmental and neurodegenerative diseases. Currently, the role of environmental factors in the modulation of the mTOR pathway remains largely unknown. The present study suggests that perinatal exposure to environmentally-relevant doses of polybrominated diphenyl ethers (PBDEs), a group of ubiquitous flame-retardants, results in long-lasting reprogramming of the mTOR pathway in mouse liver. This reprogramming includes suppression of mTORC1 and mTORC2 activity, accompanied by coordinated up-regulation of protein synthesis machinery and increased concentrations of circulating IGF-1. Further, experiments with MCF-7 breast cancer cells demonstrate that exposure to PBDEs results in fast induction of the REDD1/DDIT4 gene – a potent suppressor of mTORC1. This data indicates that the response of liver tissue to PBDE exposure during this critical developmental window is a dynamic process, and is likely triggered via a REDD1-dependent mechanism, ultimately resulting in long-lasting changes in the metabolic profile of the tissue. This study suggests that environmental exposures to brominated flame retardants may have profound and long-term effects on the central regulation hub of metabolic health, and may be implicated in the pathogenesis of the most relevant diseases of modern society.

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