A non-neuronal peripheral cholinergic signaling in metabolic homeostasis

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Cholinergic signaling from immune-derived acetylcholine has been implicated in shaping metabolic and inflammatory tone across multiple organs, suggesting that this axis may represent a broader mechanism by which the immune system calibrates tissue homeostasis under metabolic challenge. Our previous investigation have identified a non-neuronal cholinergic signaling within subcutaneous adipose and hepatic tissue niche plays a protective role against various metabolic and environmental stresses. We identified that cholinergic receptor nicotinic α2 subunit (CHRNA2) and cholinergic receptor nicotinic β2 subunit (CHRNB2) form a functional receptor in beige adipocytes, mediating a beige fat selective signaling in mice and humans, and underscoring the importance of the nicotinic acetylcholine receptor (nAChR) signaling in maintenance of energy balance. Similar cholinergic signal within the liver constitutes a cell-autonomous self-defense route against prolonged metabolic stress and alleviates symptoms of metabolic dysfunction-associated steatohepatitis (MASH). Our further investigation revealed that two families of drugs that have been used clinically could activate this peripheral cholinergic pathway in vivo and ameliorates metabolic dysfunction in mice. These findings indicate and highlight the potential of targeting this peripheral cholinergic signaling circuit against metabolic disorders in humans.