The faculty of Biotechnology and Food Engineering

Seminar

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Oncometabolites: from perception to therapeutic opportunities

Abstract

Succinate dehydrogenase (SDH) and fumarate hydratase (FH) are tricarboxylic acid (TCA) cycle enzymes while SDH is also part of the respiratory chain. Despite their key housekeeping activities, the genetic loss of FH or of any of the SDH subunits is associated with tumorigenesis. SDH or FH inactivation leads to the accumulation of succinate and fumarate, respectively. Consequently, these metabolites mediate a signaling cascade which causes the activation of hypoxia-inducible factors and the inhibition of histone and DNA demethylases, establishing pseudohypoxic and hypermethylation phenotypes. Such biochemical changes are associated with hyper-vascularization and epithelial to mesenchymal transition (EMT) resulting in increased invasiveness and motility. However, not much is known about the metabolic mechanisms which enable the survival and proliferation of TCA cycle-defective cells. Overcoming the loss of SDH and FH requires a significant metabolic rewiring as backup mechanisms for the dysfunctional TCA cycle and oxidative phosphorylation. Identifying such adaptations would reveal effective and specific vulnerabilities of these metabolically-atypical neoplasms which can serve as potential molecular targets for therapeutic intervention

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