5-MTP restores cancer cell mitochondrial dynamics and reduces oncometabolites

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We identified by comparative metabolomics a novel tryptophan metabolite i.e. 5-methoxytryptophan (5-MTP), as an endogenous COX2 suppressing factor, which inhibits cancer cell migration and invasion and reduces cancer growth and metastasis in a mouse model (Cheng et al PNAS 2012; 109:13231). It inhibits cancer cell migration and blocks epithelial mesenchymal transition (EMT) in a p38 MAPK dependent manner. Recent studies indicate that mitochondrial dynamic imbalance and accumulation of oncometabolites such as succinate due to tricarboxylic acid (TCA or Krebs) cycle enzyme (e.g. succinate dehydrogenase) mutation or defective expression drives cancer cell migration and EMT. Kuo's lab at NHRI discovered that cancer cells secrete succinate into the extracellular milieu where it enhances cancer cell migration and induces macrophage M2 polarization (Wu JY et al Mol Cell 2020; 77:213). Data from our ongoing work suggests that rebalancing mitochondrial dynamics and restoring TCA cycle thereby reducing succinate secretion is a key mechanism by which stromal cell-derived 5-MTP controls cancer growth and metastasis.