Hexosamine Pathway inhibition: one molecule able to induce a Brcaness phenotype as promising cancer therapy

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Abstract:
Emerging evidence suggests that the metabolic rewiring in cancer cells and their microenvironment is essential for tumor growth, survival, acquisition of metastatic traits and chemoresistance. A relevant role has been assigned to glucose metabolism and its downstream anabolic routes. In particular, an enhanced flux through the Hexosamine Biosynthetic Pathway (HBP) has been observed in cancer. Noteworthy, this metabolic pathway produces just one metabolite, the "sensing molecule" UDP-N-Acetylglucosamine (UDP-GlcNAc). UDP-GlcNAc is the substrate for the enzymes involved in protein N- and O-glycosylation, two important post-translational modifications (PTMs) identified in several proteins localized in the extracellular space, on the cell membrane, into the cytoplasm, nucleus, and mitochondria. Since protein glycosylation controls several key aspects of cell physiology, aberrant protein glycosylation has been already associated with different human diseases, including cancer.

Here we report the preclinical evaluation of FR054, a novel inhibitor of the HBP enzyme PGM3, with remarkable anti-cancer effects. In fact, we will describe the multiple effects of FR054 treatment in cancer cells and mice models, showing that FR054-dependent HBP inhibition, is able to counteract several cancer hallmarks either in vitro or in vivo supporting the advantage of targeting HBP for therapeutic purpose. In particular, FR054 is able to reduce homologous recombination upon chemotherapy inducing a Brcaness phenotype.

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