Tankyrases regulate anaerobic glycolysis through HIF-1α disabling

Esteban Zamudio-Martínez[1], Jerónimo Borrego-Pérez[1], José Manuel Rodríguez-Vargas[2*] and F Javier Oliver[1*]

1. Institute for Parasitology and Biomedicine “López-Neyra”, CSIC, Granada, Spain.
2. Department of Cellular Biology, University of Granada, Granada, Spain.
   * Corresponding authors

Tumor hypoxia is one of the main factors related to the increased aggressiveness and therapeutic resistance in most cancers. The oxygen-dependent protein HIF-1α and the constitutively expressed protein HIF-1β are responsible for the induction of hundreds of genes that enable cell adaptation and survival to hypoxia. Tumor cells shift their primary metabolic source from predominantly mitochondrial respiration towards increased glycolysis in order to maintain ATP levels. Under hypoxic conditions, the metabolic reprogramming regulated by HIF-1α results in the induction of multiple glycolytic components such as enzymes, glucose transporters and lactate transporters and proteins that reduce the mitochondrial oxidative phosphorylation. Tankyrase 1 (TNKS1) and tankyrase 2 (TNKS2) are two homologous proteins that belong to the Poly (ADP-ribose) polymerases (PARPs) family. Both tankyrases are gaining increasing importance due to their implication in multiple pathways including telomere elongation, regulation of signaling through Wnt/β-catenin, protein degradation, mitosis, glucose metabolism and their role in different cancer types, where tankyrases are upregulated. Besides, previous studies have revealed the implication of tankyrases in aerobic glycolysis by their relation with the glycolytic enzyme pyruvate carboxylase (PC). However, the involvement of TNKS1 and TNKS2 in anaerobic glycolysis has remained unexplored.

Our findings indicate that the loss of both tankyrases, but not their catalytic inhibition promotes a downregulation of HIF-1α, thereby impairing its activity as a transcription factor and the induction of several glycolytic proteins such as HK2, PDK1, PFKFB3-4, GLUT3 and MCT4 and proteins that inhibit mitochondrial oxidative phosphorylation (BNIP3, BNIP3-L and MXI1). The downregulation of several key glycolytic enzymes after silencing TNKS1/2 seems to affect the metabolic switch achieved during hypoxia, diminishing the glycolysis and the glycolytic capacity. This effect is also corroborated by a reduction in the levels of extracellular lactate. Taken together, these results open a new mechanism that connects tankyrases with the tumor adaptation to hypoxia and the metabolic adaptation mediated by the transcription factor HIF-1α. This finding is pivotal to identify new druggable regulators of tumor hypoxia and counteract tumor progression.