Cancer can be defined as the uncontrolled growth and division of cells, leading to tumour formation, invasion, and metastases. Unlike normal cells that require growth factor signals, tumour cells often have mutations that result in constitutively active (“always on”) signaling pathways that drive aberrant cell growth and division. In order to fulfil the high nutrient demand required for their continuous growth, tumour cells have reprogrammed their basal metabolism from an oxidative to a more glycolytic/anabolic one, even in the presence of oxygen. Major molecular mechanisms involved in the process have been identified and characterised. It was found that both oncogenes (Ras, Myc) and tumour suppressor genes (p53, RB, LKB1) impart an altered metabolic phenotype in cancer cells by regulating genes involved in central metabolic pathways.

Cyclins and cyclin-dependent protein kinases (CDKs) are important regulators of the cell cycle. In recent years, several highly effective CDK inhibitor (CDKi) drugs such as abemaciclib and palbociclib have been approved for the treatment of hormone receptor-positive, HER2-negative advanced breast cancer in combination with endocrine therapy, demonstrating substantial improvements in patient progression-free and overall survival. Many tumours eventually develop resistance to these drugs. The precise characterization of these mechanisms of resistance could lead to the identification of biomarkers predicting the clinical response to CDKis, the identification of other types of tumours also responsive to CDKis, synthetic lethality, and more precise combination therapies.

Our laboratory has collaborated with Eli Lilly Alcobendas (Madrid) and Marcos Malumbres’ Cell Division and Cancer Group at the CNIO to validate molecular targets involved in mechanisms of sensitivity and resistance to CDK4/6 inhibitors identified through a CRISPR/Cas9 library screen. One of our goals was to study how CDKis may affect tumour metabolic reprogramming. FIGURE 1 shows how both abemaciclib and palbociclib specifically target oxidative phosphorylation metabolism while leaving glycolysis unaffected.

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