Cancer can be defined as the uncontrolled growth and division of cells, leading to tumour formation, invasion, and metastasis. Unlike normal cells that require growth factor signals, tumour cells often have mutations that result in constitutively active (“always on”) signalling 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 one to a more glycolytic/anabolic one, even in the presence of oxygen, known as the Warburg effect. Both oncogenes (Ras, Myc) and tumour suppressor genes (p53, RB, LKB1) impart an altered metabolic phenotype in cancer cells through the regulation of genes involved in central metabolic pathways such as glycolytic, fatty acid metabolism, oxidative phosphorylation, nucleotide synthesis and the one carbon pool (reviewed by Gilmour & Velasco, SLAS Discov 2017). All these alterations lead tumours to rely heavily on specific metabolic pathways to obtain their energy, while using other pathways to grow in order to give them a growth advantage. This situation may leave tumour cells in a frail position under certain treatments, while normal cells may be able to compensate, adapt and survive. Our laboratory is searching for this metabolic weakness in normal cells may be able to compensate, adapt and survive.

Cancer cells preferentially use glucose for their energy needs, which is then converted to lactic acid, hence the Warburg effect. This shift is due to the overexpression of enzymes such as Pyruvate Kinase and M2 isoform, which facilitate this metabolic pathway. Pyruvate Kinase is necessary for the production of ATP and the synthesis of lactate, which is then released into the extracellular environment. This accumulation of lactate in the tumour microenvironment can have several effects on the immune system, including the induction of immune cell dysfunction and the suppression of antitumour immune responses. The release of lactate by cancer cells can also create an acidic microenvironment, which can further contribute to the promotion of tumour growth and metastasis.

The Warburg effect is not only limited to the metabolism of glucose. Other nutrients, such as amino acids, are also metabolised in cancer cells to meet the high demands of energy and cellular processes. For example, the metabolism of tryptophan, an essential amino acid, is altered in cancer cells. The enzymes involved in tryptophan metabolism, such as indoleamine 2,3-dioxygenase 1 (IDO1), are upregulated in cancer cells and can lead to the production of immunosuppressive metabolites, such as kynurenine. This can inhibit the activation and function of immune cells, including T cells, which are crucial for the surveillance and elimination of tumour cells. The presence of immunosuppressive metabolites can also create a microenvironment that is favourable for tumour growth and progression.

In summary, the metabolic reprogramming of cancer cells is a crucial aspect of cancer biology, and understanding this process is essential for the development of effective therapeutic strategies. The identification of specific metabolic vulnerabilities in cancer cells can provide new targets for therapy, allowing for the development of more effective and personalized treatments for cancer patients.