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Mathematical modelling of metabolic symbiosis in tumors

In the 1920s the findings by Otto Warburg's highlighted the fundamental differences in the metabolism of tumor cells. However, the oncogene revolution somehow pushed tumor metabolism to an ancillary level in cancer research. It is currently becoming clear that many key oncogenic signalling pathways converge to adapt tumor cell metabolism to support growth and survival, and some of these alterations seem to be required for malignant transformation [1, 2, 3].

The abnormal tumor microenvironment has a major role in determining the metabolic phenotype of tumor cells. Tumor vasculature is irregular and malfunctioning, creating spatial and temporal heterogeneity in oxygenation, pH, and the concentrations of glucose, lactate and many other metabolites. Under such varying and extreme conditions, adaptive responses are induced that contribute to the switching metabolic phenotype of malignant cells greatly influencing tumor progression. Although aerobic glycolysis (the Warburg effect) is the best documented metabolic phenotype of tumor cells, it is not a universal feature of all human cancers. Moreover, even in glycolytic tumors, oxidative phosphorylation is not completely shut down.

Hypoxic cells use glucose for glycolysis, producing large amounts of lactate and exporting it via monocarboxylate transporters (mainly the isoform MCT4), a family of proteins that when expressed in the plasma membrane are responsible for the transport of different types of molecules [4,5]. Because of the accelerated metabolism of tumor cells, these transporters are up-regulated in many different types of cancers [2,4,6]

This fact has been recognized in the last few years as opening a potential target for therapies since blocking the activity of these transporters might lead to different scenarios leading to the death of the tumor cell [2,7-10]

It has been recently demonstrated [10] that oxygenated cells within the tumor can import extracellular lactate using another transporter (MCT1) to fuel respiration, preserving glucose for use by the hypoxic cells and regulating the medium pH. This

metabolic symbiosis between oxidative and glycolytic tumor cells that mutually regulate their access to energy metabolites and pH makes the tumor progression very robust. Furthermore, it has been shown in [10] that inhibition of MCT1 induces a switch on oxidative cells from lactate-fueled respiration to glycolysis. As a consequence, hypoxic cells die from glucose starvation rendering the remaining better-oxygenated cells sensitive to irradiation and other therapies.

Similar symbiotic phenomena between the tumor and its altered microenvironment have been reported in other tumor models [11,12].

In this communication we will present a mathematical model of tumor cells behavior in vitro able to describe the glucose and lactate uptake in different scenarios. The model fits the in-vitro experiments of Ref. [10], together with other measurements reported in the literature [13], as well as our own experiments with glioma cell lines.

We will discuss how to extend the in-vitro model to incorporate other phenomena present in cancers such as hypoxia and reoxygenation. Finally, it will be examined how these mathematical models can assist in the design of optimized combination therapies with radiation and inhibitors of monocarboxylate transporters.

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