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Evolutionary dynamics of the Warburg effect: Glycolysis as a collective action problem among cancer cells

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HIGHLIGHTS

- The upregulation of glycolysis in tumors is common even when oxygen is not limiting.
- The adaptive value of this "Warburg effect" is unclear.
- Glycolysis is costly for a cell but the ensuing acidity is beneficial for the tumor.
- A collective action problem among cancer cells arises.
- Game theory shows that the acidity induced by glycolysis can explain the Warburg effect.

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ABSTRACT

The upregulation of glycolysis in cancer cells (the "Warburg effect") is common and has implications for prognosis and treatment. As it is energetically inefficient under adequate oxygen supply, its adaptive value for a tumor remains unclear. It has been suggested that the acidity produced by glycolysis is beneficial for cancer cells because it promotes proliferation against normal cells. Current models of this acid-mediated tumor invasion hypothesis, however, do not account for increased glycolysis under non-limiting oxygen concentrations and therefore do not fully explain the Warburg effect. Here I show that the Warburg effect can be explained as a form of cooperation among cancer cells, in which the products of glycolysis act as a public good, even when oxygen supply is high enough to make glycolysis energetically inefficient. A multiplayer game with non-linear, non-monotonic payoff functions that models the benefits of the acidity induced by glycolysis reveals that clonal selection can stabilize glycolysis even when energetically costly, that is, under non-limiting oxygen concentration. Characterizing the evolutionary dynamics of glycolysis reveals cases in which anti-cancer therapies that rely on the modification of acidity can be effective.

1. Introduction

1.1. The Warburg effect

The upregulation of glycolysis (the conversion of glucose to pyruvate, with consequent production of ATP, which does not require oxygen) by cancer cells, first reported by Warburg (1930), is a common feature of tumors and may seem an adaptation to hypoxia, which often occurs as a consequence of the fact that oxygen concentration decreases with distance from a capillary (Krogh, 1919, Thomlinson & Gray 1995, Dewhirst et al., 1994; Helmlinger et al., 1997). Tumors, however, consistently rely on glycolysis even in the presence of abundant oxygen (Beckner et al., 2005; Griguer et al., 2005; Kelloff et al., 2005; Rajendran et al., 2003). Since the anaerobic metabolism of glucose to lactic acid is substantially less efficient than oxidation to CO_2 and H_2O, tumor cells must increase glucose flux in order to maintain sufficient ATP production. This is the basis of the detection of glycolysis with Fluoro-deoxy-D-Glucose Positron Emission Tomography (FdG PET) (Pauwels et al., 2000; Gambhir, 2002). It is now so clear that the Warburg effect occurs even under non-limiting oxygen conditions, that FdG PET is commonly used for diagnosis and for monitoring treatment.

Why do cancer cells upregulate glycolysis? Although some organisms use glycolysis preferentially during periods of sustained growth (because the byproducts are useful as building blocks in the anabolic process), glycolysis is highly inefficient when oxygen is not a limiting factor because the anaerobic metabolism of glucose to lactic acid produces fewer ATP molecules per molecule of glucose than oxidation to CO_2 and H_2O, and therefore leads to slower proliferation. Since cancer progression is a process of clonal

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selection (Cairns, 1975; Nowell, 1976; Crespi and Summers, 2005; Merlo et al., 2006; Greaves and Maley, 2012), upregulation of glycolysis must confer a selective advantage to a cell to compensate for its slower proliferation. If it is not simply an adaptation to hypoxia, what is the adaptive value of the Warburg effect for cancer cells?

Besides its relevance to our basic understanding of cancer biology and the diagnostic and monitoring applications mentioned above, the Warburg effect has implications for treatment, as hypoxic tumors are often more invasive and metastatic than those with normal oxygen levels (Kunkel et al., 2003; Mochiki et al., 2004, Postovit et al., 2002, 2004; He et al., 2004; Buchler et al., 2003; but see also Krtolica and Ludlow, 1996), and treatments like anti-angiogenic drugs that aim at impairing the provision of oxygen to the tumor may fail if tumors can switch to glycolysis (Bergers and Hanahan, 2008).

1.2. The acid-mediated tumor invasion hypothesis

In a series of papers, Gatenby and others (e.g.: Gatenby and Gawlinski, 1996, 2003; Gatenby and Gillies, 2004, 2007) have suggested that the Warburg effect is a way for the tumor to increase its proliferation rate against normal cells, due to the fact that glycolysis induces microenvironmental acidification (Schornack and Gillies, 2003; Griffiths et al., 2001; Bhujwalla et al., 2002). An acidic microenvironment is known to confer an advantage to tumor cells by promoting the death of normal cells (Rubin, 1971; Dairkee et al., 1995; Casciari et al., 1992), since normal cells lack a mechanism to adapt to extracellular acidosis (such as mutations in p53 or other components of the apoptotic pathway, over-expression of NHE and autophagy (Park et al., 1999; Williams et al., 1999; Wojtkowiak et al., 2012)). Furthermore, acidity increases extra-cellular matrix degradation by proteolytic enzymes such as cathepsin B (Rohzin et al., 1994), which facilitates tumor invasiveness, it stimulates the release of vascular endothelial growth factor and interleukin 8 (Shi et al., 2001), which promote neo-angiogenesis, and inhibits immune function (Lardner, 2001).

In short, the hypothesis is that, even though glycolysis leads to slower proliferation for an individual cell, the consequent benefits for the tumor as a whole due to the acidification of the extracellular space (which results in toxicity for normal cells, promotes neo-angiogenesis and inhibits immune reaction) confers an overall proliferative advantage to the tumor. The hypothesis, if correct, has significant implications for cancer therapy, as manipulation of acidity could lead to anti-cancer effects.

Models of this acid-mediated tumor invasion hypothesis (Gatenby and Gawlinski, 1996; Patel et al., 2001; Smallbone et al. 2005, 2007; Basanta et al., 2008, 2011; Silva et al., 2010) show that cells with increased glycolysis will also evolve resistance to acid-induced toxicity, which can lead indeed to a significant proliferative advantage for the tumor. These models, however, make a crucial assumption: that resistance can only arise in cells with glycolysis (e.g.: Basanta et al., 2008) or that, even if resistance is not limited to hyperglycolytic cells, mutations are irreversible (e.g.: Smallbone et al., 2007; Silva et al., 2010), not allowing therefore resistant non-glycolytic cells to arise from resistant glycolytic cells. The problem that these models leave unsolved is that, by not allowing resistance to evolve in cells with aerobic metabolism or by assuming that resistant hyperglycolytic cells cannot mutate back to aerobic metabolism, they leave unexplained the very problem that the acid-mediated tumor invasion hypothesis wanted to address in the first place: why is higher glycolysis also observed under normal oxygen concentrations? In other words: what prevents a cell that forego glycolysis to invade a population?

If resistance to acidity arises in cancer cells with aerobic metabolism as well (and there is no compelling reason to assume otherwise), or if resistant cells can mutate back and abandon glycolysis (which is also reasonable), these cells would have more efficient metabolism than cancer cells with glycolysis, and could still exploit the benefit of acidity (against normal cells) induced by other cancer cells with glycolysis. Clonal selection occurs not just between cancer cells versus normal cells, but also between cancer cells with aerobic metabolism versus cancer cells with anaerobic metabolism. What maintains glycolysis (given its private cost) among cancer cells, if the hypothesized (public) benefit (acidity) accrues to all cancer cells, including those that forego glycolysis to revert to aerobic metabolism?

1.3. Glycolysis as a public goods game

The problem can be understood more easily in game-theoretic terms. Glycolysis is a private benefit under low oxygen concentrations (because it allows a cell to survive), whereas under non-limiting oxygen concentrations it is a private cost (due to the consequent inefficient metabolism); glycolysis also produces a public good (for the cancer cells): the associated acidity (against the normal cells). The benefit of acidity accrues to all tumor cells, irrespective of whether they have aerobic or anaerobic metabolism. Cells that do not pay the cost of an inefficient metabolism could free-ride on the acidity induced by neighboring tumor cells, thereby exploiting its benefit without paying the cost. In short, glycolysis can be considered a cooperative phenotype, and reverting to aerobic metabolism can be considered free-riding. This raises a classical collective action problem: why, under normal oxygen conditions, do not cells resistant to acidity forego glycolysis and revert to the more efficient aerobic metabolism, free-riding on the benefits of acidosis produced by the other cells' glycolysis? Current models of the acid-mediated tumor invasion hypothesis do not address this problem because they assume that resistance can only arise in cells with increased glycolysis or that resistant hyperglycolytic cells cannot forego glycolysis. Allowing resistant cells to revert to aerobic metabolism would make make glycolysis inefficient, and the hypothesis would fail.

The problem can be analyzed using evolutionary game theory. There are, a number of differences between the scenario of the Warburg effect and previous game theory models, which make such analysis non trivial. First, as already observed, previous game theory models of cancer progression related to the problem of glycolysis (Basanta et al., 2008, 2011) only allow the evolution of resistance in the glycolytic type. Moreover, these models assume that interactions occur between pairs of cells. In the case of glycolysis-induced acidosis, however, as acidification depends on the diffusion of the metabolic products of glycolysis, such as lactic acid and hydrogen ions (H^+), in the extracellular space (Schornack and Gillies, 2003; Griffiths et al., 2001; Bhujwalla et al., 2002), a cell's fitness depends on the collective interactions with neighboring cells, rather than on the payoff of multiple pairwise encounters with individual cells. In other words, because the products of glycolysis act as diffusible public goods, glycolysis should be modeled as a public goods game, rather than as a game with pairwise interactions; games with pairwise interactions, even when multiple interactions are allowed, do not generally have the same results as multi-player, collective action (public goods) games. An important difference is that, while in two-player non-linear games the maximum benefit for the population is achieved when all players cooperate, in multi-player games the best outcome for the population is achieved at intermediate frequencies of cooperators (Archetti and Scheuring, 2012). This, as we will see, has important implications for the dynamics of potential therapies based on the modification of acidosis.