BioSystems 127 (2015) 1–6

Contents lists available at ScienceDirect

BioSystems

journal homepage: www.elsevier.com/locate/biosystems

A reason for intermittent fasting to suppress the awakening of dormant breast tumors

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ARTICLE INFO

Article history:
Received 10 June 2014
Received in revised form 25 October 2014
Accepted 1 November 2014
Available online 4 November 2014

Keywords:
Dormant breast cancer
Fasting
Glucose tissue gradient
Oxygen tissue gradient
Anoxia
Cheap cancer treatment

ABSTRACT

For their growth, dormant tumors, which lack angiogenesis may critically depend on gradients of nutrients and oxygen from the nearest blood vessel. Because for oxygen depletion the distance from the nearest blood vessel to depletion will generally be shorter than for glucose depletion, such tumors will contain anoxic living tumor cells. These cells are dangerous, because they are capable of inducing angiogenesis, which will "wake up" the tumor. Anoxic cells are dependent on anaerobic glucose breakdown for ATP generation. The local extracellular glucose concentration gradient is determined by the blood glucose concentration and by consumption by cells closer to the nearest blood vessel. The blood glucose concentration can be lowered by 20–40% during fasting. We calculated that glucose supply to the potentially hazardous anoxic cells can thereby be reduced significantly, resulting in cell death specifically of the anoxic tumor cells. We hypothesize that intermittent fasting will help to reduce the incidence of tumor relapse via reducing the number of anoxic tumor cells and tumor awakening.

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1. Introduction

Breast cancer is still a major cause of mortality among women worldwide (Chodosh, 2011). Although its therapy has become more successful over the years and many patients will reach 5-year survival, more than 50% of deaths in patients with breast cancer occur after this 5-year survival mark (Aguirre-Ghiso et al., 2013; Klein, 2011). Folkman proposed that a tumor's size is dictated by its vasculature and that micrometastases that cannot make new blood capillaries remain clinically dormant (Folkman, 1971). Microscopic dormant breast tumors were found in 39% of autopsied women between the ages of 40 and 50 years without cancer history, although the clinical incidence of breast cancer in women in the same age range is only 1% (Nielsen et al., 1987; Zappala et al., 2013). Whereas single tumor cells may be in the blood system, only some of these circulating tumor cells may "settle to a fixed local position" and form new solid dormant tumors. In a later phase these cells could form metastases but for growth beyond the small size of a dormant tumor (diameter < 0.5–1 mm) they need angiogenesis.

Nutrient transport into the tumor is a necessary condition for tumor growth. In the absence of angiogenesis, the total number of cells in the tumor is determined by the total diffusion of oxygen (for the aerobic zone) and anaerobic substrates (including glucose) into the tumor; convection due to blood flowing into the tumor is absent. Dormant cancer lacking angiogenesis can be considered to be a tumor system of relatively low complexity as far as nutrient transport is concerned: nutrient transport from the blood vessels can then be described relatively easily, because of the relatively simple geometry of the tumor. In a "full blown" tumor with active angiogenesis, diffusion out of the blood would depend on the vascular structure, which is in tumors often very chaotic (Baish et al., 1996), many agonistic and antagonistic angiogenic factors contributing (Folkman, 2006). Modeling nutrient transport in "awakened" tumors based on the vascular structure itself would therefore be much more complex. Previously we stated that cancer is a systems biology disease (Hornberg et al., 2006), i.e., depends on a network of various factors and not always on the same network (Westerhoff et al., 2009). Besides angiogenic dormancy two other mechanisms of tumor dormancy have been distinguished, namely cellular dormancy (quiescent single cells) and immunological dormancy (Aguirre-Ghiso, 2007). At this moment it is difficult to decide which of these mechanisms has the greater clinical

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http://dx.doi.org/10.1016/j.biosystems.2014.11.001
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significance (Hensel et al., 2013). Here we will deal with a dormant tumor system at the organ level that does not grow because of the lack of angiogenesis.

From a blood vessel, small molecules will mainly be transported through tissue by diffusion. We could visualize diffusion for the fluorescent breast cancer drug doxorubicin into islands of breast cancer cells in patients (Lankelma et al., 1999; Lankelma et al., 2000). A mathematical model describing the diffusion into a cylinder of tissue from a blood vessel published by Krogh (1919), has been extended by Hill (1928),Thomlinson and Gray (1955) and Tannock (1972). Here we will focus on diffusion into a cylinder of cancer cells from well-vascularized stromal tissue present outside this cylinder. We assume that the cylinder geometry applies especially to dormant breast cancer cells that have kept a tendency to form glands, which corresponds to the observed ellipsoid cross sections (Nielsen et al., 1987). We have not observed necrosis in the images of Nielsen et al., as observed in full blown tumors (Thomlinson and Gray, 1955) and in spheroids (Olea et al., 1992). We explain this absence of necrosis by the slow dynamics and the ample time for the body to remove cellular necrosis debris.

The blood glucose concentration exceeds that of oxygen by more than the stoichiometric number 6. However, oxygen diffuses more rapidly. Examination of the mathematics shows that the depth of diffusion is a function of the product of the blood concentration and the diffusion coefficient divided by the consumption rate per cell. Using literature data for human MCF-7 breast cancer cells on consumption, diffusion in tissue and on blood concentrations of glucose and oxygen (Casciari et al., 1988; Guppy et al., 2002; Thomlinson and Gray, 1955; Vaupel et al., 1989), glucose thereby diffuses deeper into the tissue than oxygen before being completely exhausted. Consequently, next to an aerobic zone, an anoxic zone of glucose-consuming living cells will persist. Inside the circumference where glucose runs out, lies a zone of necrosis. For tumor spheroids the thickness of the viable rim decreases with the glucose medium concentration (Tannock and Kopelyan, 1986). The dormant tumor is in steady state (often for many years): in the outer core cells will proliferate (and partly disappear by shedding). The oxygen and glucose levels at the periphery determine the steady size of this 'dormant' tumor (which in reality turns over). Further away from the blood vessels the mitotic index will decrease (Hirschhaeuser et al., 2010; Rabes et al., 1979). The lack of oxygen in living cells will enhance the risk of an "angiogenic switch" (Folkman, 2002; Semenza, 2009; Vaupel et al., 1989). This can be regarded as a normal physiologic response, which also occurs in wound healing. The next step will then be an increased nutrient supply facilitated by newly formed blood vessels, and awakening of the tumor: because the influx of nutrients is increased and a proportionately larger number of living tumor cells is accommodated, which is now determined by blood flow into the tumor.

We will here formulate a hypothesis concerning a way to reduce the probability that the angiogenic switch occurs and calculate its qualifications.

2. Our hypothesis

We view the dormant tumor as an inner core of dead (necrotic) cells and cell debris that is slowly being removed, encompassed by a layer of anoxic tumor cells, which is itself surrounded by a layer of aerobic tumor cells, which is surrounded by aerobic stroma tissue (Fig. 1). The tumor is steady because for every cell in its outer aerobic layer dividing, the total amount of oxygen consumed by that layer increases, causing a cell in the innermost area of the aerobic layer to become anoxic, and a cell in the innermost area of the anoxic layer to die. Evidence for such balanced growth in angiogenic dormant tumors has been reported (Holmgren et al., 1995; Achilles et al., 2001; Folkman and Kalluri, 2004).

For the anoxic cells, we consider only glucose as the fuel for ATP generation (glutamine is present at lower concentrations and when included in the argument does not influence it essentially). We hypothesize that by temporary lowering of the blood glucose concentration the number of anoxic cells will be reduced and that this reduces the risk of awakening of the tumor because the number of cells with the potential to emit angiogenic signals is decreased.

The blood glucose concentration can be lowered 20–40% by fasting for 2–3 days (Klein et al., 1986, 1993). Fig. 1 shows our calculated decrease of the glucose and oxygen concentration from the outside of a dormant tumor to the center. For the diameter of the cylindrical tumor a clinical estimate of 0.5 mm (Nielsen et al., 1987) has been taken. The parameters have been summarized in Table 1. For the equations used and conversions of parameters, see the Appendix.

Where oxygen has run out the glucose consumption is increased to keep up with the ATP generation for the cells to

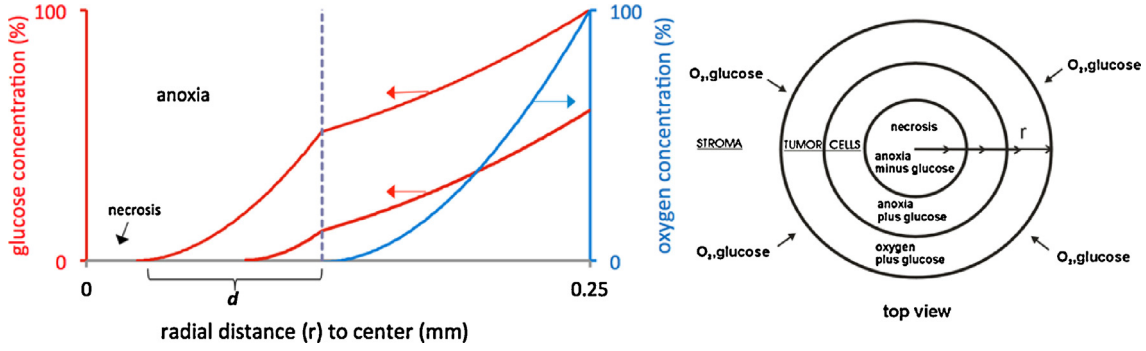

Fig. 1. The figure on the left shows the effect on reduction by fasting of the zone of living anoxic cells (as indicated by distance *d*) that have glucose around them and are thereby viable: the red line is lowered. Glucose and oxygen concentrations (left and right axis, respectively), have been calculated using the Thomlinson and Gray model and are given as percentage of "normal" blood concentrations (5 mmol/l and 0.054 mmol/l, respectively). For the model calculations, tissue diffusion coefficients and consumption parameters of MCF-7 human breast cancer cells have been taken. The lower red line represents the glucose concentration for a blood concentration of 3 mmol/l obtained during fasting. The *x*-axis gives the distance to the center of the tumor (radius chosen for calculation 0.25 mm) with cylindrical geometry surrounded by well-vascularized stroma. The figure on the right is a top view of a cylindrical tumor with zones with oxygen, anoxia plus glucose and anoxia minus glucose (necrosis). In preliminary experiments with MCF-7 human breast cancer cells, we observed a glucose consumption rate that was independent of the glucose concentration, in the range of physiological blood glucose concentrations. We therefore used a constant consumption rate per cell in the calculations. This constant consumption can be explained by the low K_M (0.1 mM) of hexokinase for glucose, causing the enzyme to work at its V_{max}, independent of the glucose concentration, above 0.1 mM (some 2% of the blood glucose concentration). Summarizing the calculations indicate that lowering the glucose concentration in the blood significantly increases the number of dangerous anoxic cells becoming necrotic.

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