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Heterogeneity of hypoxia in solid tumours and mechanochemical reactions with oxygen nanobubbles

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ABSTRACT

Tumour hypoxia leads to radio and chemotherapy resistance among cancer patients. The aim of this paper is to formulate a hypothesis on the heterogeneity of hypoxia in solid tumours. Tumour vasculature is known to be significantly variable. The great structural and functional abnormalities of tumour microcirculation cause spatial and temporal heterogeneity in its perfusion. Tumours have constantly been under the influence of pulsatile blood perfusion with variable pressure that initiates inhomogeneous erythrocyte deformation and following impact on oxygen disorder release from red blood cells into plasma within the blood vessel. Furthermore, stochastically released oxygen in tumour vessel, plasma and interstitial fluid may lead to heterogeneity of hypoxia. Under the influence of increased heterogeneity of hemodynamic force, the oxygen molecules dissolved in blood plasma are inclined to form nanobubbles (NBs) in tumour vessels. Considering the fact that tumour interstitial fluid pressure is increased compared to normal tissues, we assume that oxygen NBs may burst under the impact of shear stress. During the course of mechanochemical reaction, when a nanobubble (NB) bursts, both reactive oxygen species and ions form in various charged states. In consequence of a chain reaction, free radical oxygen molecules bind to proteins and lipids, thus reducing oxygen molecules in a chaotic manner within the tumour. The proposed hypothesis should be used as a methodical approach based on the simultaneous ultrasound imaging diagnostic techniques and therapy, regarding the mechanochemical effect on NB conglomerates with drugs in the tumour.

Introduction

The pathogenesis of tumour hypoxia is one of the molecular basis of cancer process. The condition when oxygen supply does not entirely cover tumour needs, and so some tumour areas are lack of oxygen is referred to as hypoxia. O.H. Warburg (Nobel Laureate in medicine) has postulated that normal cells transform into malignant due to defects in the aerobic respiratory pathways and malignant cell respiration is impaired. A. Szent-Györgyi (Nobel Laureate in medicine) has also viewed cancer as originating from the insufficient availability of oxygen. Oxygen on its own is able to inhibit malignant cell proliferation by interfering with anaerobic respiration [1].

The greater part of all solid tumours originally arises as a cancer cell conglomerate with no supporting vasculature. At this stage cancer cells pass the nutrients in and wastes out through the cell membrane via simple diffusion. Further cell development, such as proliferation, invasion and metastasising requires direct blood supply to maintain the uptake of nutrients. The tumour growth depends in many ways on the intensity of its angiogenesis.

Tumour vessels differ both structurally and functionally from normal blood vessels. The tumour vasculature is tortuous, irregular branching and has a highly variable vessel diameter. Blood vessels supplying the tumour are significantly heterogeneous and chaotic as well as the tumour itself. Apparently, delivering nutrients through newly formed tumour vessels leads to variable oxygen, glucose, ATP and other metabolites distribution. This initiates heterogeneous spatial and temporal patterns of hypoxia in both tumour and its microenvironment [2]. In consequence, the tumour blood flow differs widely in speed, direction and perfusion rate. The speed of blood flow along the tumour exterior is higher than in its core in some cases, whereas in others it is vice versa. In addition, around 30% of arterial blood passing through the tumour may not be consumed by cancer cells [3,4].

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In soft tissues, tumour vessels are constantly exposed to mechanical forces, including fluid shear stress, hydrostatic tension and compression pressure. Fluid shear stress is one of the major forces that cells are subjected to, and yet much more is still unknown about fluid shear stress effects on tumour cells. Although, cancer cells may experience shear stress generated by slow fluid flows in the vascular microenvironment (0.5–30 dyn/cm^2) as well as the tumour microenvironment (0.1 dyn/cm^2). Cancer cells may transiently encounter greater fluid shear stress up to 1000 dyn/cm^2 in turbulent flows within the heart and large vessel bifurcation. Endothelium that lines the interior surface of tumour blood vessels may contain fenestrations, which are involved in increased vessel permeability and result in plasma splits into the tumour interstitial, contributing to high interstitial pressure up to 60 mmHg. However, the tumour interstitial pressure increases within the tumours core and drops down to exterior. Furthermore, the tumour interstitial pressure can also fluctuate, causing the tumour microvascular pressure to change. The combined action of interstitial and microvascular tumour pressure through increased vessel permeability is able to equalise the perfusion pressure between the afferent and efferent tumour blood vessels that leads up to vascular stasis without signs of actual vasoconstriction [5,6]. One of the few questions that has yet remained open is how arterial and venous perfusion plays role in tumours, regarding hypoxia and other metabolic processes.

The oxygen dissolved in blood plasma has a few ways to be transported to human body tissues. It has been shown that 98% of oxygen are carried via erythrocytes and only 2% remain unbound flowing in plasma. The latter one could be possibly referred to as molecules of gaseous oxygen (O_2) with size 0.3 nm that are mixed up in blood and available to take part in respiration for the most of host cells [7].

In recent years, much research has been devoted to studying the properties of nanoscopic bubbles (<200 nm in diameter) and clusters for dissolved gases in liquids. The disturbance of water structure in the contact area induces the formation of gas nanobubbles (NBs). Along with that, the bubbles have already been registered in the blood during ultrasound irradiation [8]. Factors triggering disturbance of water structure and forming NBs include mechanical or ultrasonic vibration, electron beam, etc. The mechanochemical effect should be explained as the conversion of mechanical into chemical energy and vice versa. The prior studies have indicated that minor change of mechanochemical reactions in water can initiate gas nanobubble (NB) formation. The high oxygen solubility of bubbles is beneficial for hypoxic tissue oxygenation. With respect to vascular gas embolism, the NBs are clinically safe. Microvessel embolism was not observed in the case when gas NBs were used in contrast to ultrasonography with sufficiently low pressure amplitudes of ultrasound [9,10].

NBs are gas filled cavities with internal pressure at least equal to that of the external environment. Due to hydration shell and electric charge on the NB surface, heterogeneous gas diffusion rate and heterogeneity of hypoxia in tumour, each bubble is surrounded by an interface with different properties than the bulk solution. The NBs are in constant flux with gas molecules both leaving and entering continuously. They are also under excess pressure as the surface tension causes a tendency to minimise their surface area, and hence volume. These NBs may have far reaching physicochemical, medical and biological effects [11–13].

Mechanical stresses against the vessel wall are able to set of mechanochemical reactions that generate radicals and ions via breaking weak bonds through shock-induced NB collapse [14]. Mechanochemical basis is the epigenetic factor of cell and tissue regulation [15]. The role of mechanochemical reactions in origin of oxygen NBs and heterogeneity of tumour hypoxia has been paying close attention in this work. Earlier, it has been found that hypoxic regions are heterogeneously disseminated in at least 50–60% of tumour mass. Hypoxia can also occur when the gap between a cancer cell and diffused oxygen molecules becomes widened, but still a few cells in a direct contact with the capillary could reach the gas. Besides, transient hypoxia is thought to be a critical factor that triggers the increased glucose uptake and its fermentation to lactate in cancer cell metabolism, which is also recognised as Warburg effect. Nowadays, there is enough evidence to show the key importance of heterogeneity in hypoxia initiation, as a consequence of both variable tumour vasculature and blood flow [16].

The heterogeneity of hypoxia in cancer cells introduces significant challenges in designing effective treatment strategies [17]. Understanding processes underlying the heterogeneity of hypoxia formation in tumours would presumably allow us to find new approaches in overcoming chemo and radiotherapy resistance. The aim of this paper is to formulate a hypothesis on the role of mechanochemical reactions in origin of oxygen NBs and heterogeneity of hypoxia in solid tumours.

Hypothesis

The hypothesis is presented as a sequence-based description of chaotic-assisted mechanisms that cause heterogeneous formation of oxygen NBs in blood that leads to heterogeneous oxygenation and hypoxia in some components of the tumour and its microenvironment. The model scheme for heterogeneity of hypoxia in solid tumour pathogenesis and mechanochemical reactions with oxygen NBs is depicted in Fig. 1.

Heterogeneity of vascular structure and hemodynamics

As mentioned before, tumour is chaotic structure, and so is its vascular hemodynamics. Tumour blood vessels have constantly been under the influence of great irregular hemodynamic forces, which are general for the whole body. The cardiac cycle acts on hemodynamic forces in a tumour vessel, thus rising up both shear stress and hydrostatic pressure during ventricular systole and then dropping the pressure down in diastole. Shear stress is a tangential frictional force on the endothelial layer (intima), while circumferential stress is circumferential distension of blood pressure acting on vessel wall (intima, media and adventitia). As opposed to shear stress, hydrostatic pressure is the perpendicular force exerted by the volume of blood on vessel wall that contains it. Hydrostatic pressure and shear stress are not the only force that exists in a blood vessel such as hydraulic pressure, osmotic pressure, etc. In addition, hemodynamic forces are complex regulators of endothelial gene expression [18].

Most of tumour vessels are not perfused continuously. The blood flow may follow different pathways in the same vessel over a few minutes. The tortuous shape of tumour vessels is one of the main reasons why hemodynamic forces have a heterogeneous impact on a vessel wall throughout the cardiac cycle.

Heterogeneous shape of erythrocyte conglomerates

Previously mentioned features of vascular hemodynamics will initiate inhomogeneous change in the shape of erythrocyte conglomerates. Naturally, erythrocytes are the major oxygen carriers in the human body. Haemoglobin is a metalloprotein discovered in human erythrocytes that binds oxygen molecules under the influence of high partial pressure of oxygen (e.g. pulmonary venule) and releases the gas molecules when the partial pressure of oxygen is low (e.g. capillary in metabolically active tissue). Passing through a tumour, erythrocytes have been exposed to