

Conference Paper

Hypoxia Immunity, Metabolism, and Hyperthermia

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Hypoxia is common in solid tumors and in many other disease states such as myocardial infarction, stroke, bone fracture, and pneumonitis. Once hypoxia has developed, the undernourished and hypoxic cells trigger signals in order to obtain new blood vessels to satisfy their increasing demands and to resolve hypoxia. The principal signal activated is an ancestral oxygen sensor, the hypoxia inducible factor (HIF). After its nuclear translocation, HIF triggers a series of mediators that recruit, into the hypoxic milieu, several immature myeloid, mesenchymal, and endothelial progenitors cells. Resident and recruited cells participate in the processes of neoangiogenesis, for resolving the hypoxia, while at the same time trigger an inflammatory reaction. The inflammatory reaction has as primary end point, the repair of the damaged area, but if an insufficient production of resolvins is produced, the inflammatory reaction becomes chronic and is unable to repair the damaged tissue. In this brief overview, we will show the differences and the similar events present in cancer, myocardial infarction, and stroke. Furthermore, the metabolic alterations produced in the tumor by hypoxia/HIF axis and the consequences on hyperthermic treatment are also discussed.

1. Introduction

The local inflammatory reaction is characterized by an initial increase in blood flow to the site of injury, by increased vascular permeability, and by an ordered influx of different effector cells, recruited from the peripheral blood and bone marrow to the site of lesion [1].

Another characteristic of the inflammatory reaction is the presence of hypoxia and its modulation of innate immunity [2].

In this overview, we will analyze the influence of the hypoxic state on inflammation and compare its interaction in diverse disease states including cancer. Interestingly, the

body's response to hypoxia in different pathological situations seems to be quite similar (see Box 1).

2. Hypoxia as a Homeostatic Response

Once hypoxia has developed, the undernourished and hypoxic cells present trigger signals, in order to obtain new blood vessels, and satisfy their ever-increasing demands. The principal signal activates an ancestral oxygen sensor, the hypoxia inducible factor (HIF). HIF is a conserved mechanism of defense present in mammals, aimed at reestablishing a supply of oxygen and nutritive substances. After its nuclear translocation, HIF triggers a series of mediators such as

Hypoxia → HIF → SDF-1-VEGF → CECs-EPCs-MSCs-MDSCs → Neutrophils →
Macrophages → repair/or remodeling → Hypoxia resolution

Box 1: In this box is illustrated the homeostatic circuit tending to eliminate hypoxia.

vascular endothelial growth factor (VEGF) and chemokines such as stromal derived growth factor-1 (SDF-1), which orchestrate a series of processes able to recruit, from bone marrow, into the hypoxic (tumour) milieu, several immature myeloid, mesenchymal, and endothelial progenitors cells [2–6]. The bone-marrow-derived cells are of 4 types.

- (a) Circulating Endothelial Cells (CECs) [7, 8].
- (b) Endothelial progenitor cells (EPCs), which are precursors of blood vessels [9, 10].
- (c) Mesenchymal stem cells (MSCs) [11, 12].
- (d) Immature myeloid derived cells (MDSCs) [13–16].

CECs and EPCs are cells able to form new blood vessels. MDSCs concur with them to support and promote all the reactions useful to angiogenesis but are unable to form the neovessels alone. MSCs have the ability to transform into fibroblasts, to coordinate the inflammatory reaction, and also to support cells of the stroma [17]. In addition, MSCs play an important role in the repair of tissues with lesions and fractures. In the tumour, the excessive presence of IL-1 and PGE2 triggers an autocrine process that leads to tumor progression [18]. The behavior of MSCs in tumour tissue is different than that in myocardial infarction and stroke, where they cooperate to repair the lesion and reduce the inflammatory reaction. In fact, they behave differently in the primary tumour than in metastases, and usually give rise to the tumor-associated fibroblasts (CAFs) and pericytes [19] that ultimately form a favorable stroma more useful to tumor progression and with immunosuppressive activity.

When MSCs become triggered by HIF, they participate in the repair of several diseased tissues and organs such as in myocardial infarction [4], stroke [20], fractures [21], rheumatoid arthritis [22], Alzheimer's diseases [23], Parkinson's diseases [24], ulcerative colitis [25], and kidney disease [26].

In a certain sense, it is possible to demonstrate that the reaction of the organism to a pathogen or other danger signal is a normal law of homeostasis and is tightly regulated (see Box 1).

In fact, four to six hours after the start of the ischemic or hypoxic state, partly resident neutrophils provided by MDSCs begin to produce a series of free radicals and proteases. In both the heart and the brain, areas of ischemia show these reactions which initially seem harmful, somehow sharpening the event [11, 27]; however, after this cleaning operation they help to decrease the inflammatory reaction. In both stroke and myocardial infarction they collaborate through several known mechanisms [11, 27].

Neutrophils have a very limited life span, going rapidly into apoptosis and releasing among various other products

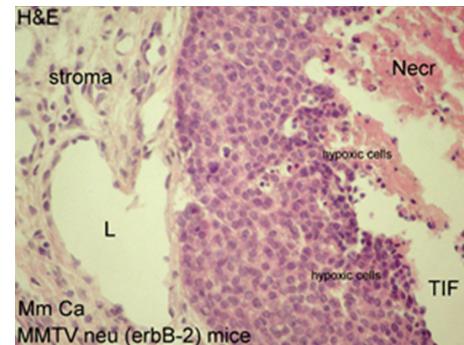


FIGURE 1: Zones of hypoxia adjacent to zones of necrosis. (kindly supplied by I Freitas, University of Pavia, Italy).

lactoferrin. Lactoferrin has the ability to decrease the recruitment and the transmigration of neutrophils, permitting the arrival of macrophages. Macrophages not only act as scavengers but also produce abundant immunosuppressive cytokines (TGF- β ; IL-10). Macrophages also produce decoy receptors of chemokines that participate to further decrease the inflammatory reaction [26, 28]. A more recently discovered class of substances able to reduce the inflammatory response have been called resolvins [29, 30]. In summary, the termination or the partial reduction of inflammation coincides with the return of oxygenation, the coordination of leukocyte recruitment followed by macrophage recruitment, and finally the production of anti-inflammatory factors including resolvins.

3. Tumour Hypoxia

Hypoxia is common in solid tumors, and areas deprived of oxygen and nutrients can develop in many different zones of the tumor, including those with strong vascularization (Figure 1). One of the reasons for its persistence is that neoplasia grows faster and at a pace not proportional to the neoangiogenesis [31–33]. This persistence creates a vortex that continues to recruit neutrophils and MDSCs from bone marrow [34]. In the tumour microenvironment, MDSCs transform into type 2 macrophages, the so-called M2 that produces an excess of molecules such as PGE2, TGF- β , and IL-10. These kinds of molecules can disorient the immune system to the point of making it ineffective [35]. Furthermore the tumour is unable to produce resolvins in an adequate concentration [36–38] for at least two reasons.

- (a) There is no an adequate concentration of EPA and DHA in the cell membranes (principal substrates for resolvins).

- (b) There is an increase in COX-2 enzymes leading to overproduction of PGE2 [37, 38], which are not precursors for resolvins.

This is a circuit that continues to feed itself on the basis of a normal homeostatic response of the organism. Tumours follow the general pathways of several diseases in which hypoxia is implicated (i.e., myocardial infarction, stroke, etc.), but differs from them significantly in the persistence of this hypoxia and the lack of the off switch (resolvins) (Figures 2 and 3).

Another factor that seems to maintain the inflammation is the osmotic pressure. The overproduction of VEGF induced by HIF leads to increased vascular permeability, with loss in the interstitial tissue of albumin and other proteins. This loss, leads to an increased osmotic pressure that elicits the release of proinflammatory cytokines by macrophages [39–41]. This factor alone would justify the use of hyperthermia for its ability to decrease the interstitial fluid pressure [42, 43].

Tumour vasculature is not necessarily derived from endothelial cell sprouting; instead, cancer tissue can acquire its vasculature by alternative mechanisms, such as vasculogenic mimicry (VM). VM is the hypoxia-adaptation mechanism of tumour vascularisation. Hypoxia-induced VM plays an important role in tumour progression [44, 45].

4. Hypoxia Metabolism

HIF not only plays an important role in inflammation but also determines the metabolic conversion in tumours to anaerobic glycolysis, the so-called Warburg effect. This increased consumption of glucose and its incomplete and inefficient metabolism is due at least to two factors:

- an increase in membrane receptors for glucose (Glut-1 membrane protein),
- Blocking of pyruvate dehydrogenase and suppression of pyruvate conversion to acetyl CoA [46–48].

5. Hyperthermia and Immunity

Can hyperthermia be used to modify this destructive and cancer-promoting circuit of hypoxia, inflammation, and then hypoxia? Is it possible that hyperthermia can affect HIF expression and, beyond that, immunity against malignancy?

This association between hyperthermia and tumor hypoxia and pH response has been known since 1990, in large part because of the work of Koutcher and Gerweck on glioblastoma and other tumours [49, 50]. What is more is that hyperthermia's activity as a radiation sensitizer is well known [51–55]. Hyperthermia, in almost every way it has been applied, consistently seems to affect immunity through several known mechanisms [56–58]. Hyperthermia enhances the antigenic presentation to effector cells, recruiting macrophages, natural killer cells, regulatory cells, and neutrophils to the tumour area [56–58]. The association with radiotherapy and the favorable changes to the tumour microenvironment by hyperthermia, as outlined by Muthana

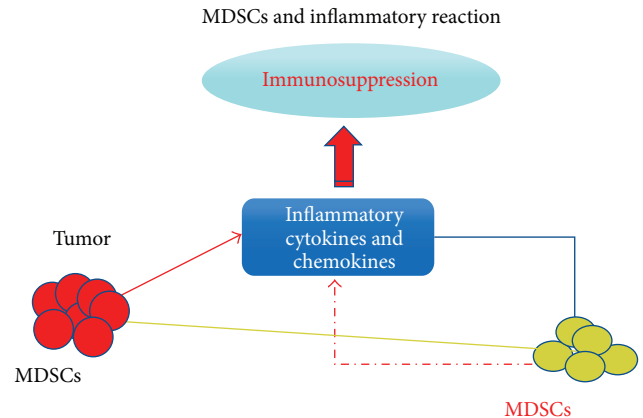


FIGURE 2: The genesis of inflammation and the circuit triggered by tumor and MDSCs are tentatively illustrated.

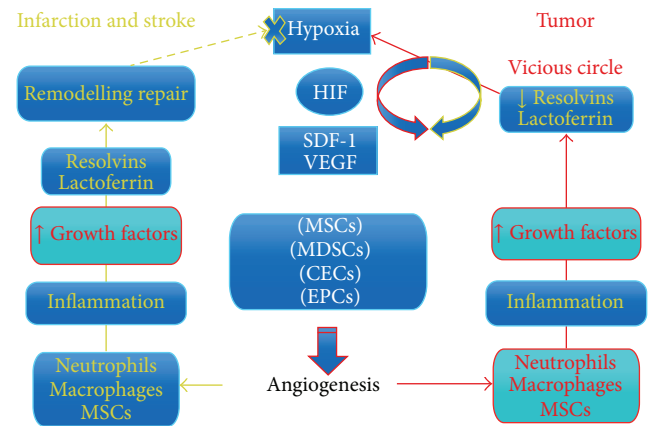


FIGURE 3: In this figure, the common response of the organism to hypoxia is illustrated together with the different responses to infarction, stroke, and cancer. It should be noted that many processes are common, but in cancer hypoxia is not completely resolved. This persistence of the hypoxic environment creates a vicious cycle that ultimately sustains the inflammation.

et al. can affect regulatory cell behavior and macrophage activity [59]. In fact, the concurrent use of hyperthermia with radiotherapy can decrease the recruitment of regulatory cells, compared to hyperthermia alone, and also the behaviour of macrophages seems to be affected by this association, ultimately decreasing their M2 types [60]. The macrophage programming in the tumour microenvironment is a hallmark of cancer, with its autosustaining abilities regarding inflammation [58]. The increase of heat shock protein (HSP) induced by hyperthermia [61], particularly HSP 70, has been found to act as a recognition structure for natural killer (NK) cells, increasing their activity [62, 63]. *In vivo* hyperthermia triggers innate and adaptive immunity aiding in tumour eradication [64, 65].

6. Conclusions

The explanation of these specific components of tumour biology in this way is not meant as an oversimplification

but is meant as an effort to show that tumour biology is not all chaotic, but that they follow some normal routes of repair. Tumours exploit some of the weaknesses of the body and profit from normal attempts of the body to repair and recover organ integrity and functionality. In the works of Lowe and Storkus, by minimizing exposure to risk factors that contribute to chronic inflammation and reconditioning the patient into a state of acute inflammation, we could have a significant decrease in cancer incidence and improvements to life prolongation [66]. Hyperthermia in this context can have a significant role as an inducer of acute inflammation [64, 65].

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