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Review

Hypoxia and hypoxia-inducible factors in myeloid cell-driven host defense and tissue homeostasis

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ABSTRACT

The impact of tissue oxygenation and hypoxia on immune cells has been recognized as a major determinant of host defense and tissue homeostasis. In this review, we will summarize the available data on tissue oxygenation in inflamed and infected tissue and the effect of low tissue oxygenation on myeloid cell function. Furthermore, we will highlight effects of the master regulators of the cellular hypoxic response, hypoxia-inducible transcription factors (HIF), in myeloid cells in antimicrobial defense and tissue homeostasis.

Contents

Introduction

There is a constantly increasing interest in understanding the composition of the microenvironment in inflamed and infected tissues and in deciphering the effect of local environmental signals on immune cells (Matzinger and Kamala, 2011; Renz et al., 2011). In addition to chemokine and metabolic signaling, the impact of tissue oxygenation and hypoxia on immune cell function attracted the scientific interest (Dehne and Brune, 2009; Eltzschig and Carmeliet, 2011; Nathan and Cunningham-Bussel, 2013; Nizet and Johnson,

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Table 1
Tissue oxygen levels in inflamed, infected and cancerous tissue.

Condition	Tissue oxygen level	References
Inflamed gut mucosa	<10 Torr (~1.3% O_2)[b]	Campbell et al. (2014), Karhausen et al. (2004)
Peritonitis (*E. coli*)	~6 Torr (~0.8% O_2)[a]	Sawyer et al. (1991)
Gastric mucosal tissue during *E. coli* sepsis	~10 Torr (~1.3 O_2)[a]	Payne and Bowen (1981)
Acutely inflamed skin (intradermal injection of purified protein derivative)	~20 Torr (~2.7% O_2)[a]	Abbot et al. (1994)
Chronic inflamed skin (chronic venous ulcers)	~37 Torr (~5% O_2)[c]	Schreml et al. (2014)
Infected subcutaneous foreign body (*P. mirabilis*)	~0 Torr (0% O_2)[a]	Niinikoski et al. (1972)
Infected subcutaneous foreign body (*E. coli*)	~8 Torr (~1.1% O_2)[a]	Raju et al. (1976)
Infected skin (*S. pyogenes, L. amazonensis*)	<10 Torr (~1.3% O_2)[b]	Araujo et al. (2012), Peyssonnaux et al. (2008)
Infected skin (*L. major*)	~21 Torr (~2.8% O_2)[c]	Mahnke et al. (2014)
Subcutaneous cancer (MB49)	<10 Torr (~1.3% O_2)[a]	Aly et al. (2006)
Infected lung (*Mycobacterium tuberculosis*)	<10 Torr (~1.3% O_2)[b] ~80 Torr (~10.8% O_2)[a] ~2 Torr (~0.3%)[a]	Aly et al. (2006), Harper et al. (2012), Heng et al. (2011), Via et al. (2008)
Infected lung (*Aspergillus fumigatus*)	<10 Torr (~1.3% O_2)[b]	Grahl et al. (2011)
Schistosoma mansoni-infected tissue (liver, spleen, lung)	<10 Torr (~1.3% O_2)[b]	Araujo et al. (2010)
Pyelonephritis (*E. coli*)	<10 Torr (~1.3% O_2)[a]	Melican et al. (2008)
Inflammatory joint disease	~8–78 Torr (~1.1–10.5%)[a]	Treuhaft and DJ (1971), Lund-Olesen (1970)
Artheriosclerotic plaque	<10 Torr (~1.3% O_2)[a,b]	Bjornheden et al. (1999), Sluimer et al. (2008)
Various cancerous tissues	~10 Torr (~1.3% O_2)[a]	Reviewed in Vaupel et al. (2007)

[a] Polarographic electrode measurements.
[b] Staining of hypoxic areas after injection of 2-nitroimidazol derivatives.
[c] Luminescence-based optical imaging.

2009; Schaible et al., 2010; Sitkovsky and Lukashev, 2005; Strehl et al., 2014).

Hypoxia in inflamed and infected tissues

Seminal studies using electrographic, Clark-type microelectrodes demonstrated that wounded, infected and inflamed tissues display low oxygen tensions (pO_2) (Abbot et al., 1994; Aly et al., 2006; Melican et al., 2008; Niinikoski et al., 1972; Payne and Bowen, 1981; Raju et al., 1976; Sawyer et al., 1991) whilst healing was promoted by enhanced oxygen availability (Hunt et al., 1975; Knighton et al., 1984, 1986; Rabkin and Hunt, 1988; Remensnyder and Majno, 1968). In addition, 2-nitroimidazol derivatives were used to mark tissues with oxygen levels below ~10 Torr (~1.3% O_2). After injection of these compounds into animals, they form adducts with proteins at low pO_2 that can be detected by subsequent immunohistochemical methods in tissue specimens (Arteel et al., 1995; Gross et al., 1995). This technology revealed that inflamed gut (Campbell et al., 2014; Karhausen et al., 2004), *Schistosoma mansoni*-infected tissue (Araujo et al., 2010), *Streptococcus pyogenes*- and *Leishmania amazonensis*-infected skin (Araujo et al., 2012; Peyssonnaux et al., 2008) and *Mycobacterium tuberculosis*- or *Aspergillus fumigatus*-infected lung tissue (Grahl et al., 2011; Harper et al., 2012; Heng et al., 2011; Via et al., 2008) are hypoxic. Although this technique is powerful in detecting tissues that display very low oxygen tensions it does not allow for repetitive, direct quantification of tissue oxygen levels. These limitations can be overcome by oxygen-detection systems based on the luminescence quenching of dyes. These dyes can be immobilized into sensor foils and allow for 2D *in vivo* quantification of oxygen concentrations in conjunction with ratiometric or luminescence based real-time read out systems. Luminescence-based optical oxygen imaging techniques can be easily performed, allow for repetitive non-invasive analysis of tissue oxygen levels without consuming oxygen which might affect precision at low oxygen levels (reviewed in Wang and Wolfbeis (2014)). These approaches were validated recently in humans (Babilas et al., 2008, 2005; Schreml et al., 2011) and mice (Hofmann et al., 2013). We used this system to monitor oxygen levels of infected skin tissue in mice over time. We resorted to a mouse model of self-healing cutaneous leishmaniasis (Bogdan, 2012; Mougneau et al., 2011; Sacks and Noben-Trauth, 2002). When *Leishmania (L.) major*-induced lesions of self-healing C57BL/6 mice reached their maximum size, the infected tissue displayed low oxygen levels (pO_2 ~21 Torr; ~2.8% O_2) (Mahnke et al., 2014). Most interestingly, resolution of the wound was paralleled by an increase of lesional pO_2 (Mahnke et al., 2014).

In addition to microbial associated inflammatory responses, a variety of other inflammatory processes is characterized by infiltrating immune cells and local hypoxia (Table 1). E.g. diseases such as rheumatoid arthritis or inflammatory bowel disease have been linked to a hypoxic microenvironment (Campbell et al., 2014; Doust, 1951; Karhausen et al., 2004; Lund-Olesen, 1970; Stevens et al., 1991; Treuhaft and DJ, 1971). Furthermore, expanding tumours outgrow their oxygen supply and therefore tumor-associated macrophages actively move to, reside and function in a hypoxic environment (reviewed in Murdoch et al. (2004), Vaupel et al. (2007)). In addition to ischemia induced by reduced blood perfusion (Biswas et al., 2010), atherosclerotic lesions associated with the invasion of monocytes and macrophages have been shown to be hypoxic (Bjornheden et al., 1999; Sluimer et al., 2008). These findings expand the range of conditions in which a potential crosstalk between immune cells and severe hypoxia signaling might be present (Table 1).

Regulation of tissue oxygen in infected and inflamed tissues

The mechanisms driving low tissue oxygenation and the normalization of tissue oxygen levels in the course of inflammation remain in parts elusive. Cutaneous injection of Freund's adjuvant resulted in a reduced local tissue perfusion and concomitantly reduced tissue oxygen levels (Abbot et al., 1994). Using a mouse model of bacterial pyelonephritis Melican et al. demonstrated that the infection triggered a local activation of clotting. This resulted in diminished tissue perfusion that prevented systemic spreading of the bacteria (Melican et al., 2008). Blood neutrophils attracted by perivascular macrophages (Abtin et al., 2014) might play an important role in the development of local tissue hypoxia since neutrophil-derived serine proteases and extracellular nucleosomes enhance plasmatic coagulation. This impairs tissue perfusion and facilitates the compartmentalization of bacteria on the site of infection (Massberg et al., 2010). In addition, the cellular oxygen demand of the pathogens and/or infiltrating leukocytes might also contribute to the low oxygen levels on site. Campbell et al. demonstrated that transmigrating PMNs depleted the mucosal