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Letter to the Editor

HYPOXIA IMPACTS THE DYNAMICS AT PLAY IN INFECTION, IMMUNITY, AND INFLAMMATION

Maria Giuseppa Onesta*

Unipolar Spinal Unit, Cannizzaro Emergency Hospital, Catania, Italy.

**Correspondence to*:
Dr. Maria Giuseppa Onesta,
Unipolar Spinal Unit,
Cannizzaro Emergency Hospital,
Catania, Italy.
e-mail: mp.onesta@gmail.com

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INTRODUCTION

Several diseases can cause decreased oxygen tension in tissue, resulting in hypoxia that can impact the dynamics of infection, the immune system, and the inflammatory system (1). Hypoxia is a pathological state caused by a lack of oxygen in the entire organism, which can be generalized or affect a specific tissue. It can play a role in regulating both the host and the pathogen during disease by contributing to infection and inflammation and affecting immune response.

Efficient oxygenation of tissues allows for the maintenance of normal physiological aspects of metabolic activity. In humans, the alveolar partial pressure of O2 (pO2) is 100-110 mmHg (2) and sufficient oxygen supply allows for the maintenance of physiological normoxia, in which oxygen delivery to tissue is equal to or slightly greater than metabolic demands (2). Both the innate and adaptive immune systems defend tissue that is directly exposed to invasive pathogens, environmental toxins, and pollutants.

The typical feature of tissue hypoxia is the pallor of the skin and/or mucous membranes in certain areas. It can cause syncope with sudden and temporary loss of consciousness characterized by rapid onset, short duration, and complete and spontaneous recovery. Hypoxia occurs in both healthy conditions and diseases. Infections with invasive microorganisms in the lung can lead to activation of innate immune defense mechanisms to combat the threat of microbes or their derivatives, an action aimed at maintaining pulmonary homeostasis (3). In the lung, impaired mucociliary clearance can lead to bacterial colonization, chronic mucosal inflammation, and tissue necrosis.

Hypoxia can also occur in various physiopathological states. Transcription factors can mediate pulmonary hypoxia; for example, hypoxia-inducible factor (HIF) is a heterodimeric transcription factor that regulates tissue oxygen homeostasis and regulates gene expression to adapt to the oxygen-deficient environment. HIF is degraded by enzymes such as proline and asparagine hydroxylase. There are three isoforms of HIF expressed by alveolar epithelial cells of the lung: HIF-1, HIF-2, and HIF-3. In long-term hypoxia, HIF-2 and HIF-3 proteins remain stable, while the increase in HIF-1 protein is temporary, in anticipation of one transition to another (4).

DISCUSSION

Hypoxia, infection, immunity, and inflammation are closely related in various biological and pathological processes. Hypoxia can occur in localized areas, such as within tumors or infected and inflamed tissue, or systemically. Hypoxia

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tends to restore oxygen balance, such as increased red blood cell production or angiogenesis. When tissue is infected with subsequent inflammation, there is reduced blood flow with limited oxygen supply and a reduced immune response (5).

The invasion and multiplication of pathogens (bacteria, viruses, fungi, parasites) during infection activates the immune response to defend the organism, with the activation of macrophages, neutrophils, and lymphocytes. This immune response is closely linked to both inflammation and hypoxia. In fact, pathogens often thrive in hypoxic environments, such as in abscesses or tissue infections. Hypoxia affects the response of immune cells; it is known that macrophages can adopt different activation states, such as pro-inflammatory or anti-inflammatory, depending on the hypoxic environment, influencing the effectiveness with which they eliminate infections (6). There is evidence that some viruses, such as human immunodeficiency virus (HIV) and influenza, exploit hypoxic conditions to replicate more efficiently, demonstrating that hypoxia plays a crucial role in these conditions.

Immunity can be both innate or adaptive; innate immunity mainly involves phagocytes, such as neutrophils and macrophages, while B cells and T cells play a crucial role in adaptive immunity. Hypoxia can alter the functions of these immune cells. For example, HIFs help immune cells adapt to low oxygen levels by regulating energy metabolism and survival (7). In tissues where chronic hypoxia occurs, immune cells may become dysregulated, contributing to immune evasion by pathogens. Conversely, hypoxia can increase the killing capacity of immune cells in the event of acute infection by increasing their oxidative capacities.

The activation of immune cells leads to the release of cytokines and the recruitment of other factors that aid in tissue repair and pathogen elimination. Inflammation can cause localized tissue hypoxia due to increased metabolic demands on immune cells and physical damage to blood vessels (8). Hypoxia amplifies inflammatory responses, enhancing the release of pro-inflammatory cytokines, such as TNF and IL-1β, through HIF pathways. Immune cells in hypoxic environments switch to glycolytic metabolism with energy production without oxygen, which can alter their function.

Chronic inflammation and prolonged hypoxia can lead to pathological conditions such as fibrosis, autoimmune diseases, and cancer. In inflammatory diseases such as rheumatoid arthritis, inflammatory mediators reduce blood flow, causing hypoxia, which further promotes cytokine release and exacerbates the inflammatory response. Hypoxia alters the function of immune cells by promoting metabolic reprogramming (9). For example, HIF-1 in macrophages can improve their ability to kill bacteria by increasing their production of reactive oxygen species (ROS). However, prolonged hypoxia in chronic diseases, such as chronic infections, can lead to immune suppression by promoting regulatory immune cells such as T regulatory cells (Tregs), which reduce inflammation and suppress anti-pathogen immunity. Certain diseases, including cancer, often have a hypoxic core, which creates an immunosuppressive environment. Hypoxia-induced changes in immune cells, such as T-cell exhaustion, allow tumor cells to evade the immune system. Chronic infectious diseases, including tuberculosis, or chronic viral infections can create a hypoxic environment in which immune cells are less effective. This makes infections difficult to clear and leads to prolonged inflammation and tissue damage.

Therapeutically, targeting HIF or using oxygen therapy could modulate the immune response under hypoxic conditions. Manipulating the metabolic state of immune cells, such as switching from glycolysis to oxidative phosphorylation, could improve immunity in hypoxic tissue environments such as chronic infections and tumors.

CONCLUSIONS

Hypoxia, infection, immunity, and inflammation form a set of biological responses where each component influences the others. The study of these pathophysiological responses can lead to a greater understanding of hypotoxic phenomena, including chronic infections, which may help in the treatment of patients with respiratory difficulties due to infectious diseases.

Conflict of interest

The author declares that they have no conflict of interest.

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