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Review Article

Gene Expression Control in Hypoxic conditions involved in Wound Healing

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Abstract

Haemostasis, inflammation, proliferation, and remodelling are some of the phases that make up the complex process of wound healing, which is controlled by numerous signals. The main cell types involved in wound healing are keratinocytes, endothelial cells, macrophages, and fibroblasts. Since cells detect hypoxic conditions and alter their gene expression in response, hypoxia plays a crucial role in this process. This investigation examined the in vitro expression of 77 genes in human keratinocytes (HaCaT), microvascular endothelial cells (HMEC-1), differentiated macrophages (THP-1), and dermal fibroblasts that are involved in angiogenesis, metabolism, cell development, proliferation, and death (HDF). The results showed that hypoxia-induced gene expression profiles were cell-type specific. Most of the genes regulated by hypoxia in HMEC-1 and differentiated THP-1 encode angiogenesis-related proteins or cytokines and growth factors. Hypoxia mostly influenced the expression of genes encoding proteins involved in cell metabolism in HaCaT and HDF. This research may contribute to a greater understanding of the molecular mechanisms by which a hypoxic environment affects wound healing (Canals et al., 2022).

Eukaryotes frequently experience various types of stress. Eukaryotes engage stress-response pathways and control gene expression to adapt to such conditions. Transcription, RNA processing, RNA transport, and translation are only a few of the numerous processes involved in eukaryotic gene expression. We concentrate on both transcriptional and post-transcriptional controls of gene expression under hypoxic settings in this review study. The transcriptional controls mediated by different transcription factors, such as Hypoxia-Inducible Factors (HIFs), are described in the first section of the review. In the second section, we discuss how splicing factors and their kinases regulate RNA splicing in hypoxic environments. This article reviews and discusses recent research on the two gene expression mechanisms in hypoxic environments (Nasako et al., 2020).

Keywords: Hypoxia, Transcription, HIFs, Splicing, SR proteins, SR protein kinases

INTRODUCTION

Haemostasis, inflammation, proliferation, and remodelling are the four overlapping phases that usually make up the complicated multistep and multicellular biological process that is wound healing. Hypoxia and inflammation are mutually dependent, and inflammation brought on by hypoxia plays a role in the progression of many different human illnesses. Chronic wounds and slow wound healing are directly related to ongoing inflammation. On the other hand, tissue hypoxia or the stabilisations of hypoxia-dependent transcription factors are typically present in inflammatory conditions. Growth factors, cytokines, chemokines, matrix metalloproteinases (MMPs), and extracellular macromolecules are just a few of the signals that control the healing process. Innate immune cells, including neutrophils and macrophages, are drawn to the site of a skin injury to clear away any cell debris and release mediators that can stimulate keratinocytes, endothelial cells, and fibroblasts. To ensure an adequate blood supply for tissue repair and wound healing, angiogenesis is essential. Beginning with those found at the edges of wounds,

endothelial cells proliferate, destroy basement membrane, and migrate to form new blood vessels (Ishii et al., 2004). Collagen, elastin, proteoglycans, and other glycoproteins of the extracellular matrix are produced by fibroblasts and mature outside of cells. Some fibroblasts transform into myofibroblasts, which cause the wound to contract. For the purpose of regenerating a confluent epithelium, keratinocytes multiply and move from the edges of the wound. All cell types' migration and proliferative processes are controlled by intricate systems of growth factor and chemoattractant inhibition and stimulation (Takano et al., 2016).

In fact, the main cell types engaged in wound healing processes are keratinocytes, endothelial cells, macrophages, and fibroblasts. These cells interact with one another to regenerate healthy tissue. Since it is necessary for epithelialization, angiogenesis, collagen deposition, and infection resistance, oxygen is a fundamental regulator of organised wound healing. The main cause of hypoxia in wounds is blood vessel damage, which impairs oxygen delivery to the injury site. Additionally, the quick recruitment of inflammatory cells raises the oxygen need for phagocytosis and microbial eradication. Persistent hypoxia, insufficient wound healing, or chronic wounds are all caused by a reduction in oxygen delivery. When cells experience hypoxia, they can change their metabolism and their gene expression to help them survive. Hypoxia-inducible factor 1 (HIF-1), which controls the transcription of hundreds of genes that aid in cell survival in hypoxia, is the primary mediator of the transcriptional response. Hypoxia affects several genes that are involved in metabolism, cell growth, and angiogenesis, but various cell types have varied hypoxia-responsive gene expression patterns. The objective of this study was to evaluate how four different cell types involved in wound healing responded genetically to hypoxia (Difilippantonio et al., 2003). Angiogenesis, metabolism, cell growth and proliferation, apoptosis, transcription, and signalling were identified as key cell processes/functions important for wound healing. Through the use of cell models of keratinocytes, endothelial cells, macrophages, and fibroblasts, the expression of 77 genes involved in these processes was examined in vitro, which focuses on the cell-specific reactions to hypoxia, could shed light on how different cell populations regulate their gene expression profiles and the function of hypoxia in wound healing (Yao et al., 2014).

Most living things are exposed to oxygen because it makes up 20.9% of the earth's atmosphere. Cells benefit from the efficient energy production of mitochondria, which uses oxygen. Oxidative stress harms cells and results in cell death; however oxygen can also cause this. As a result, animals have evolved a variety of coping mechanisms to deal with varying oxygen conditions. The hypoxic response, which is produced when cells are exposed to a low oxygen environment, is one such tactic. The body's tissues develop hypoxic conditions because oxygen is not readily available everywhere. This environment (also known as physiological normoxia), in which a fairly low oxygen concentration is maintained in relation to the atmosphere, represents the typical oxygen status of each tissue and cell. In contrast, cells and tissues are deprived of oxygen at high altitudes and under pathological circumstances like ischemia, leading to severely hypoxic conditions. In order to survive, organisms must react appropriately to such circumstances (Kondo et al., 2015). Under hypoxic conditions, the hypoxia response is a systemic process that controls numerous cellular processes in order to preserve homeostasis. By increasing the amount of red blood cells or blood arteries, this reaction improves oxygen delivery. It also modifies energy consumption, boosts cell motility, and promotes cell adaptation and cell survival. In some clinical situations, the hypoxic response speeds up the evolution of disease while providing protection against stressors. Hypoxic situations develop in ischemia diseases and disorders, including malignancies, inflammatory diseases, heart attacks, and stroke. A bad prognosis is caused by the hypoxia response, which helps cancer cells survive and encourages their invasion and spread (Mikkonen et al.., 2010).

Different processes in the human body detect oxygen levels. The carotid body, a component unique to humans and found in the carotid artery, monitors blood oxygen and carbon dioxide levels. The carotid body gets agitated when it notices a drop in blood oxygen levels and transmits a signal to encourage breathing, increasing the amount of oxygen taken in from the atmosphere. Oxygen is necessary for the action of a class of enzymes known as 2-oxoglutarate (2-OG)-dependent oxygenases, which are inhibited when oxygen is scarce. Prolyl-hydroxylase PHD, a 2-OG-dependent oxygenase that inhibits Hypoxia-Inducible Factor, is one of the best studied oxygenases (HIF). These enzymes adjust their enzymatic activity in response to variations in the oxygen concentration. In particular, they are more active when there is oxygen present and less active when there isn't (Uehara et al., 2002).

DISCUSSIONS

HIF is a key role in these parameters and controls hypoxic reactions. This factor is made up of the subunits and. It was first discovered that the HIF- subunit is a nuclear factor that binds to the 3’ enhancer region of the EPO gene. HIF consists of two subunits (HIF- and ARNT2) as well as three subunits (HIF-1, HIF-2, and HIF-3). HIF-1 and HIF-2 subunits have a domain structure and are members of the bHLH-PAS protein family, but there is only about 50% homology at the amino acid level between them. In the nucleus, HIF- and HIF- heterodimerize to promote the expression of many genes. HIF-1 has been found to target more than 100 genes. The biological roles of these genes, such as metabolism, angiogenesis, anti-apoptosis, and cell motility, can be categorised. To properly adapt cells to hypoxia,

certain biological mechanisms are crucial. HIF-1 and HIF-2 are two of the several HIF subunits that have undergone substantial research. These two subunits perform a wide range of distinct and frequently overlapping roles. The fact that the expression of the component is controlled in a way that depends on oxygen is one of HIF's key characteristics. The ubiquitin-proteasome pathway breaks down HIF- under normoxic conditions, where oxygen is readily available. HIF- is stabilised in contrast when oxygen is scarce, or under hypoxic conditions. HIF- was considered to sense oxygen because to its oxygen-dependent expression and activation. HIF- includes an oxygen-dependent degradation domain, which is important for the oxygen-dependent expression of this subunit, according to biochemical investigations. The oxygen-dependent degradation domain comprises proline residues, which are essential for this oxygen requirement, according to later investigations. These hydroxylated proline residues control what happens to HIF-. HIF-'s proline residues are hydroxylated by the enzyme prolyl hydroxylase domain-containing protein (PHD). It is a member of the family of 2-OG-dependent oxygenases and needs co-factors like Fe2+, 2-OG, and oxygen to function. PHD serves as an oxygen-sensing molecule since it needs oxygen as a co-factor (Sussan et al., 2005).

While it has been noted that a number of genes experience AS when exposed to hypoxia, very few research have focused on the underlying molecular processes. Using in vitro splicing tests, the molecular mechanism behind hypoxia-dependent AS of IPAS in HeLa cells was examined. This demonstrated that HIF-1-regulated hypoxia-induced expression of Cdc2-like kinase 1 (CLK1) increases. In hypoxic cells, HIF-1 promotes CLK1 mRNA expression, which in turn causes an increase in CLK1 protein expression. AS patterns are induced by CLK1's hyperphosphorylation of SR proteins in hypoxic conditions. The family of splicing factors known as SR proteins, which are expressed in all metazoans, play a variety of roles in both constitutive and alternative splicing.

CONCLUSION

This work describes the changes in gene expression in cell populations involved in wound healing in response to hypoxic conditions. Depending on the kind of cell, its purpose, and its energy needs, cells go through a range of biological changes when exposed to hypoxia. Different cell types responded differently to hypoxia, with HaCaT and differentiated THP-1 displaying a larger number of regulated genes and HDF and HMEC-1 showing a lower number. The majority of the regulated genes in HaCat and HDF fall within the category of glycolytic metabolism. Most of the time, hypoxia in these cell types causes the production of the genes required to switch cells from oxidative to glycolytic metabolism. Contrarily, in HMEC-1, the majority of genes that are influenced by hypoxia encode proteins that are involved in angiogenesis. It appears that endothelial cells need autocrine signals to maintain angiogenesis during hypoxia. In differentiated THP-1, a significant number of genes encoding angiogenesis-related proteins were also up-regulated. This is not shocking considering that macrophages are known to be essential in the regulation of angiogenesis through the secretion of molecules. In differentiated THP-1 and HMEC-1, genes encoding cytokines/chemokines and growth factors were also primarily modulated. The fact that VEGF-A gene expression increased in all the cell types involved in wound healing, however, shows that hypoxia specifically induces this important growth factor. When a wound is healing, hypoxia is important. To begin further in-depth research on the underlying processes, it may be helpful to know which genes in cell types involved in skin healing are altered by hypoxia.

Because both transcriptional and post-transcriptional processes are involved in cellular responses to hypoxia, they are intricate. The importance of HIFs and other transcription factors for the hypoxia response is widely acknowledged. Additionally, mounting data indicates that pre-mRNA splicing is crucial for gene expression under hypoxia. Numerous genes have been shown to undergo hypoxia-dependent processes in addition to IPAS. The molecular processes that control AS that is dependent on oxygen tension are still unknown. Along with SR proteins, hnRNPs, a sizable protein family, may also play a role in hypoxia-dependent AS. To further understand these mechanisms, additional research is needed to find pre-mRNAs with cis-acting components and trans-acting splicing regulators. Additionally, it is necessary to investigate how transcription and splicing interact in hypoxia cells. These studies are necessary to fully comprehend the cellular hypoxia response and are expected to advance our understanding of tumour gene expression regulation and adaptation. We really expect that our analyses may aid in the discovery of fresh targets and potential cancer treatments.

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