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Review

Myeloid cell dysfunction and the pathogenesis of the diabetic chronic wound

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ABSTRACT

Diabetes can promote a state of chronic inflammation associated with serious complications that are difficult to treat, including ulceration of the lower extremities and chronic wounds. Chronic wounds are often incurable and contribute to both a reduced quality of life for patients and an enormous burden for healthcare services. In diabetes, the inflammatory response early in wound healing is inappropriately amplified and prolonged, leading to the persistent presence in the wound of vastly elevated numbers of dysfunctional, hyperpolarised macrophages that fail to transition to a pro-healing phenotype. Recent evidence suggests that systemic chronic inflammation induces intrinsic defects in monocytes *via* chromatin modifications that may pre-programme monocytes to a pro-inflammatory phenotype, while the local wound environment inhibits differentiation to a pro-healing phenotype. Current understanding remains incomplete, and careful dissection of how local and systemic inflammation combine to negatively influence myeloid cell development will be key to developing effective therapies aimed at healing the diabetic wound.

1. Introduction

Inflammation is a tightly regulated and complex process that occurs in response to tissue injury or infection. Local signals released by cells near damaged tissue or in response to invading pathogens trigger an inflammatory cascade that involves the recruitment of leucocytes from circulation, and the activation of both resident and recruited cells to release pro-inflammatory cytokines and chemotactic factors that further amplify the inflammatory response [1]. The careful control of all phases of inflammation, from initial release of factors promoting inflammation at the site of injury to the eventual resolution of inflammation and the elimination of inflammatory cells from the site of tissue damage, is vital to restore homeostasis. The dysregulation of inflammation has severe consequences: tissue damage associated with untreated chronic inflammation occurs in diseases such as rheumatoid arthritis [2] and inflammatory bowel disease [3], while persistent inflammation has long been associated with increased cancer risk [4]. Chronic inflammation is also a hallmark of diabetes and its complications [5]. Global diabetes incidence is currently over 347 million and increasing rapidly, with the number of children diagnosed at an all-time high [6]. Although the majority of diabetic complications are manageable, they are not curable [7], and chronic wounds are among the least treatable, often resulting in lower limb amputation [8]. Dysregulated inflammation is one of the primary pathologies associated with chronic wounds, thus an understanding of the causes and consequences of dysregulated inflammation in diabetes is key if effective therapies are to be developed.

There are two main types of diabetes, both of which are characterised by chronic hyperglycaemia. Type 1 diabetes (T1D) is caused by the autoimmune-mediated loss of function of the pancreatic beta cells responsible for insulin production, which leads to an inability to regulate blood glucose levels and chronic hyperglycaemia. T1D accounts for 10% of all diabetes cases in the world and is primarily diagnosed in individuals under the age of 40. The remaining 90% of cases involve type 2 diabetes (T2D), which is primarily diagnosed in adulthood. T2D is characterised by reduced insulin production and insulin resistance, and is caused by a combination of genetic and environmental factors, with obesity accounting for 80–85% of the risk of developing T2D [6,9]. Incidence of both T1D and T2D is increasing [10,11], although T2D accounts for the overwhelming majority of new diabetes cases, and has shown the most dramatic rise in developing nations [6,9,12]. North American expenditure on diabetes in 2013 was $263 billion, while Europe spent $147 billion. This represents approximately 10%

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of their respective healthcare budgets, and it is estimated that this figure will rise to 17% of the healthcare budget by 2035/36 [13].

Hyperglycaemia associated with T1D and T2D causes widespread complications in a range of tissues and organs through a variety of mechanisms [14]. Common diabetic complications include retinopathy, cardiovascular disease, nephropathy and neuropathy [9]. Both cardiovascular disease and neuropathy contribute to the development of the diabetic ulcer along with dysregulated inflammation. Decreased sensory perception in the extremities that arises as a result of diabetic neuropathy leads to a dampening in the sensation of injuries; this means that relatively minor damage to the feet and legs can lead to an infected wound that, due to widespread defects in the wound healing process and the increased susceptibility of diabetic individuals to bacterial infection, fails to heal and develops into a chronic wound that is highly pro-inflammatory [15]. There is no cure for the diabetic foot ulcer, and they are estimated to result in 60% of non-traumatic lower limb amputations performed each year [16]. The combination of the deleterious effect of diabetes on patient health and the increasing cost to health services means that there is a pressing need to understand the underlying mechanisms of chronic inflammation and impaired healing.

This review will discuss current knowledge of the mechanisms involved in dysregulated inflammation in diabetes, with a particular emphasis on the consequences of chronic inflammation for wound healing. A key question in the field is whether myeloid cells and their precursors undergo intrinsic changes in the diabetic environment that lead to aberrant development and differentiation, or whether the local wound environment is the key factor in inducing chronic inflammation in the diabetic wound. This review will discuss the interplay between these two factors and how improved understanding of the multifaceted impact of inflammation on diabetic wound healing is leading to the development of therapies targeted at the diabetic chronic wound.

2. Myeloid cell subsets: marker expression, function and origin

Myeloid cells develop from haematopoietic progenitors in the bone marrow (BM) and are released into the bloodstream upon maturation. There are two main subsets of the myeloid population: monocytes, which are mononuclear cells that differentiate into macrophages in tissues, and granulocytes, which are also known as polymorphonuclear (PMN) cells. Both myeloid cell subsets are recruited to the cutaneous wound early in the first, inflammatory phase of healing, and play a crucial role in eliminating bacteria and debris from the wound site immediately after tissue damage has occurred, and in the successful resolution of the inflammatory phase and transition to the stages of healing in which tissue remodelling and eventual resolution of the healing response occur (recently reviewed in [17]). However, in patients with diabetes, the development of a hyperinflammatory environment is characterised by heightened and prolonged presence of both PMNs and macrophages, which appear to be dysfunctional in a variety of assays, such as apoptosis and phagocytosis (reviewed in [15]).

Both T1D and T2D are associated with dysregulation of myeloid cells, both in circulation and in the diabetic wound. The majority of work on impaired healing and chronic inflammation in diabetes has been carried out in mouse models. T1D is predominantly modelled by the streptozotocin-induced mouse [18] and by the non-obese diabetic (NOD) mouse [19]; while T2D models include the leptin mutant mouse (*ob*/*ob* or *Lep*$^{-/-}$) [20,21], and the leptin receptor mutant mouse (*db*/*db* or *Lepr*$^{-/-}$) [22,23]. As in human T1D, the mouse models of T1D are induced by destruction of the beta cells in the pancreas [18,24]. Likewise, both T2D models mirror human T2D as increased adipose tissue leads to macrophage activation and insulin resistance, which triggers diabetes [25]. Characterisation of myeloid cell populations from the blood and bone marrow of diabetic mice remains incomplete, but recent advances related to the identification and description of myeloid cells in diabetes, and how these differ both from those found in wild-type mice and those found in other models of chronic inflammation, are described below (see also Fig. 1 and Table 1).

2.1. Heterogeneity of myeloid cell populations in inflammation

'Granulocyte' is the collective term given to neutrophils, basophils and eosinophils, which are released into circulation as mature cells with a relatively short lifespan and distinct functions (reviewed in [26]). During homeostasis, neutrophils comprise approximately 50–70% of the human circulating leucocyte population, while in mice they are less abundant and represent approximately 10–25% of leucocytes. Circulating neutrophil numbers increase markedly and rapidly during the inflammatory response. Recent work has suggested that two distinct neutrophil populations may exist in acute inflammation that can be distinguished by size, granularity and differences in levels of marker expression. This suggests a difference in activation state [27]. Eosinophils and basophils are much less abundant in circulation and are relatively poorly characterised, although both cell types have been implicated in asthma and allergic responses (reviewed in [26,28]).

Within the monocytic population, two main classes of monocyte have been characterised: a less abundant, 'patrolling' population that migrates primarily to non-inflamed tissues, and a much larger population of monocytes that expands in number in response to inflammation and is recruited into injured tissue where they differentiate into activated macrophages (Fig. 1) [29]. Cells belonging to this latter population play a crucial role in both chronic and acute inflammation, as well as in the resolution of infection through the release of cytokines. Like neutrophils, they are phagocytes that can eliminate cellular debris and pathogens, such as in the inflammatory phase of wound healing [30]. The origin of macrophages present in peripheral tissues varies depending on context. It has recently been suggested that tissue-resident macrophage populations are laid down during embryonic development and maintain their numbers without contribution from blood monocytes [31]. Macrophages present in the cutaneous wound during inflammation primarily arise through differentiation of monocytes recruited from circulation and derived from the BM [32]. This is in contrast to the 'type 2' inflammation that arises in response to allergy or helminth infection, where proliferation of tissue-resident macrophages and not recruitment of BM-derived macrophages is believed to underlie macrophage accumulation [33].

Myeloid cell populations are not homogenous, and it is likely that their contribution to the initiation and resolution of inflammation in all contexts is equally heterogeneous. While some studies have sought to identify the impact of diabetes on blood myeloid cell populations, understanding is still relatively limited in comparison to other inflammatory conditions. Furthermore, although it is known that BM-derived myeloid cells recruited to the wound from circulation play a crucial role in the healing process [32,34,35], the precise role of different myeloid subsets, including tissue-resident macrophages, and how these roles overlap remains poorly understood, as does the consequence of their dysregulation in diabetes. Only through carefully untangling the web of interactions between granulocytes, monocytes, macrophages and other cell types will we be able to identify suitable targets for therapies aimed at healing the diabetic chronic wound. A key step in this process is the definition of myeloid cell subsets and how they are impacted by the chronic inflammatory state of diabetes, as well as identification of