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Review Article

Importance of insulin resistance to vascular repair and regeneration

Richard M. Cubbon *, Ben N. Mercer, Anshuman Sengupta, Mark T. Kearney

Multidisciplinary Cardiovascular Research Centre, LIGHT Laboratories, The University of Leeds, Leeds LS2 9JT, UK

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ABSTRACT

Metabolic insulin resistance is apparent across a spectrum of clinical disorders, including obesity and diabetes, and is characterized by an adverse clustering of cardiovascular risk factors related to abnormal cellular responses to insulin. These disorders are becoming increasingly prevalent and represent a major global public health concern because of their association with significant increases in atherosclerosis-related mortality. Endogenous repair mechanisms are thought to retard the development of vascular disease, and a growing evidence base supports the adverse impact of the insulin-resistant phenotype upon indices of vascular repair. Beyond the impact of systemic metabolic changes, emerging data from murine studies also provide support for abnormal insulin signaling at the level of vascular cells in retarding vascular repair. Interrelated pathophysiological factors, including reduced nitric oxide bioavailability, oxidative stress, altered growth factor activity, and abnormal intracellular signaling, are likely to act in conjunction to impede vascular repair while also driving vascular damage. Understanding of these processes is shaping novel therapeutic paradigms that aim to promote vascular repair and regeneration, either by recruiting endogenous mechanisms or by the administration of cell-based therapies.

Contents

* Corresponding author. Fax: +441133437738.
E-mail address: r.cubbon@leeds.ac.uk (R.M. Cubbon).

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Introduction

A broad spectrum of overlapping clinical disorders, including obesity, prediabetes, and diabetes mellitus (DM), is associated with impaired metabolic action of the principal glucose-lowering hormone insulin, referred to as "insulin resistance." Diabetes is associated with a twofold increase in major cardiovascular events, such as myocardial infarction (MI) or stroke; these events occur approximately 15 years earlier than in patients without DM [1,2]. However, cardiovascular risk is also significantly elevated in the prolonged prediabetic phase, before the development of sustained hyperglycemia [3]. The International Diabetes Federation suggest that by 2030 the number of diabetes sufferers globally will rise to 552 million, an increase of 50% compared with current data; these figures rise to approximately 1 billion people if impaired glucose tolerance is also included [4]. In clinical practice we are aware that the prevalence of comorbid DM in patients suffering MI or heart failure is increasing, with contemporary observational studies quoting prevalence in excess of 25% [5,6]; these patients experience mortality double that of those without diabetes [7,8]. Furthermore, even after excluding those with known DM or hyperglycemia, the majority of patients sustaining MI exhibit DM or prediabetes, when comprehensively assessed [9]. Clearly, the impact of insulin resistance is likely to become increasingly important to the primary and secondary prevention of cardiovascular disease, and outcome data suggest current strategies are failing to adequately address this issue.

The principal process underlying the cardiovascular risk associated with insulin resistance is atherosclerosis, a phenomenon of arterial wall inflammation and lipid accumulation, progressing toward unstable plaque formation with abrupt vascular occlusion [10]. A clustering of proatherosclerotic factors promoted by insulin resistance and obesity, known as the "metabolic syndrome," is implicated in atherogenesis even before the onset of established diabetes (marked by sustained hyperglycemia) [11]. Dysfunction and damage to the arterial endothelium is thought to act as a key initiating event in atherogenesis, in part by reducing the bioavailability of the key antiatherosclerotic radical nitric oxide (NO) [10,12]. Indeed, impaired NO-dependent vasomotion is present in patients across the spectrum of insulin resistance [13–15]. Moreover, insulin induces NO generation in the vascular endothelium and glucose uptake in metabolic tissues via analogous signaling cascades, the activity of which is commonly impaired in insulin resistance, linking "endothelial dysfunction" and metabolic insulin resistance [16].

Although our understanding continues to evolve, it is apparent that endogenous vascular repair can mitigate vascular injury, thus retarding atherogenesis and promoting repair of injured tissue in the context of vascular occlusion [17,18]. Given the persistently poor cardiovascular outcomes of patients with insulin-resistant syndromes [8], promotion of cardiovascular repair may therefore represent an attractive therapeutic paradigm. However, it has also emerged that disease processes associated with vascular injury are also commonly linked with diminished indices of vascular repair [19]. This review will detail our current understanding of how insulin resistance adversely influences endogenous vascular repair and regeneration, in particular focusing on molecular mechanisms that may be amenable to novel pharmacologic or gene- or cell-based strategies.

Vascular repair and regeneration

Before discussing the impact of insulin-resistant syndromes upon vascular repair and regeneration, it is important to clarify the distinct, but overlapping, phenomena involved in the repair of injured conduit vessels and the regeneration of vasculature in injured tissue. In this review, vascular repair is predominantly used to denote the reendothelialization of established conduit vessels injured by pathologic processes, such as atherosclerosis, and therapeutic revascularization procedures. The precise mechanisms of vascular repair remain incompletely defined and clearly depend on the context of injury, though relying upon both the direct incorporation and the paracrine activity of multiple populations including local vascular cells, circulating leukocytes, and progenitor cells [20–22]. An emerging body of work suggests that endogenous bone marrow-derived cells do not directly incorporate as endothelial or smooth muscle cells within murine conduit vessel neointima to any meaningful extent [23–25]. However, this is disputed by other authors [18] and by no means discounts an important paracrine contribution of bone marrow-derived cells in stimulating and orchestrating local vascular cell-mediated repair. Furthermore, a number of reports suggest some contribution of bone marrow-derived cells to human small-vessel endothelium after sex-mismatched cardiac or bone marrow transplantation [26,27]; further work is required to resolve these disparities.

The process of vascular regeneration is in many respects more complex, because a hierarchical branching vascular plexus must develop concurrent with the repair or replacement of a wider tissue parenchyma. The term *angiogenesis* is often incorrectly used as a synonym for vascular regeneration, when in fact it describes the more defined process of sprouting of neovessels from existing vasculature [28]. This is distinct from the process of *vasculogenesis,* in which neovessels form de novo from circulating stem/progenitor cells; agreement exists as to the role of this process in utero, although there remains no direct evidence of its role in adulthood. Finally, *arteriogenesis* refers to the maturation of neovessels into conduit vessels, resulting in luminal enlargement and vessel coverage with pericytes and vascular smooth muscle cells [29]. This process is important in achieving sufficient tissue perfusion and remains poorly understood, although endothelial shear sensing and recruitment of circulating leukocyte subsets have been implicated as contributing [30,31].

Importantly, vascular (re)generation is not a homogeneous process, invoking differing mechanisms and mediators according to the context of vessel formation. Angiogenesis is often distinguished as being developmental (occurring in utero) or pathological (in response to an insult to established tissue), although there remains mechanistic overlap between the two [28]; this review focuses on pathological angiogenesis, given its relevance to insulin-resistant diseases. The most profound stimulus for angiogenesis is hypoxia, which activates tissue oxygen-sensing cascades, subsequently altering expression of a host of angiogenesis-modulating molecules, including increased transcription of the prototypical proangiogenic mediator vascular endothelial growth factor (VEGF) [32]. It is also clear that inflammation can also promote angiogenesis, though we now recognize there to be very close links between hypoxia and inflammation, such that angiogenesis in the context of inflammation may invoke hypoxic