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MORPHOLOGICAL CHARACTERISTICS OF MYOCARDIAL ANGIOGENESIS AND ITS IMPAIRMENT IN EXPERIMENTAL DIABETES

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ANNOTATION

Diabetes mellitus (DM) represents one of the most significant global health challenges, not only due to its metabolic derangements but also because of its strong association with cardiovascular diseases. Myocardial ischemia in the diabetic heart is accompanied by profound alterations in angiogenesis, impairing tissue perfusion and regenerative responses. Experimental models of diabetes, including chemical induction and genetic approaches, have provided important insights into the structural and molecular mechanisms underlying impaired myocardial angiogenesis. This article reviews the morphological and molecular features of myocardial angiogenesis in experimental diabetes, focusing on endothelial dysfunction, alterations in capillary density, ultrastructural damage, and dysregulation of signaling pathways such as VEGF, HIF-1α, and PI3K/Akt. Understanding these mechanisms is crucial for the development of novel therapeutic strategies to improve myocardial recovery in diabetic ischemic heart disease.

Keywords: diabetes mellitus, myocardial ischemia, angiogenesis, VEGF, HIF-1α, endothelial dysfunction.

ANNOTATSIYA

Qandli diabet (QD) nafaqat metabolik buzilishlar, balki yurak-qon tomir kasalliklari bilan kuchli bog‘liqligi sababli ham eng dolzarb global sog‘liq muammolaridan biridir. Diabetik yurakda ishemiya angiogenez jarayonining chuqur buzilishlari bilan kechadi, bu esa to‘qimalarning qon bilan ta’minlanishini va regeneratsiya imkoniyatlarini cheklaydi. Ushbu maqolada eksperimental diabet modellarida miokard angiogenezining morfologik va molekulyar xususiyatlari, endotelial disfunktsiya, kapillyar zichligining pasayishi, ultrastruktura darajasidagi o‘zgarishlar va VEGF, HIF-1α hamda PI3K/Akt yo‘llarining buzilishi tahlil qilinadi. Ushbu mexanizmlarni tushunish diabetik yurak ishemiyasi sharoitida yangi terapevtik yondashuvlarni ishlab chiqishda muhim ahamiyatga ega.
Kalit so‘zlar: qandli diabet, miokard ishemiyasi, angiogenez, VEGF, HIF-1α, endotelial disfunktsiya.

АННОТАЦИЯ

Сахарный диабет (СД) является одной из самых значимых глобальных проблем здравоохранения не только из-за метаболических нарушений, но и вследствие тесной связи с сердечно-сосудистыми заболеваниями. Миокардиальная ишемия при диабете сопровождается глубокими нарушениями ангиогенеза, что ухудшает перфузию тканей и регенераторные процессы. В данной статье рассмотрены морфологические и молекулярные особенности ангиогенеза миокарда при экспериментальном диабете, включая эндотелиальную дисфункцию, снижение плотности капилляров, ультраструктурные повреждения и дисрегуляцию сигнальных путей VEGF, HIF-1α и PI3K/Akt. Понимание этих механизмов имеет ключевое значение для разработки новых терапевтических стратегий при ишемической болезни сердца у пациентов с диабетом.
Ключевые слова: сахарный диабет, ишемия миокарда, ангиогенез, VEGF, HIF-1α, эндотелиальная дисфункция.

INTRODUCTION

Cardiovascular complications remain the leading cause of morbidity and mortality in patients with diabetes mellitus, accounting for nearly two-thirds of deaths associated with the disease (1). Among these complications, ischemic heart disease (IHD) combined with diabetic cardiomyopathy exerts particularly deleterious effects on cardiac structure and function, ultimately leading to heart failure and poor clinical outcomes. In the context of diabetes, not only macrovascular changes such as accelerated atherosclerosis but also microvascular dysfunction critically contribute to the pathogenesis of myocardial ischemia (2).

A growing body of experimental and clinical evidence indicates that impaired angiogenesis is a central mechanism underlying the inadequate adaptive response of the diabetic myocardium to ischemia. Under normal physiological conditions, myocardial ischemia stimulates the formation of new collateral vessels via two complementary processes: angiogenesis, which involves the sprouting of capillaries from preexisting vessels, and arteriogenesis, characterized by the remodeling and enlargement of preexisting arterioles into functional conductance arteries (3). These processes are essential for restoring blood supply to ischemic myocardium and preserving cardiomyocyte viability.

However, in the diabetic state, multiple interrelated factors—such as endothelial cell dysfunction, reduced nitric oxide bioavailability, increased oxidative stress, accumulation of advanced glycation end products (AGEs), and chronic low-grade inflammation—significantly blunt both angiogenesis and arteriogenesis (4,5). This results in insufficient collateral vessel development, poor perfusion of ischemic areas, and a greater propensity for myocardial necrosis and fibrosis. Moreover, experimental studies have demonstrated that pro-angiogenic signaling pathways mediated by vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1α (HIF-1α), and other growth factors are markedly attenuated in diabetic myocardium, further aggravating ischemic injury (6).

Given these pathological features, the investigation of angiogenesis in experimental models of diabetes is of paramount scientific and clinical importance. Morphological analysis provides insight into the structural alterations of myocardial microcirculation, while molecular studies reveal key signaling pathways that are disrupted in diabetes. Together, these approaches can enhance our understanding of the disease process and potentially guide the development of novel therapeutic strategies aimed at restoring angiogenic competence. Such therapies may include the use of gene therapy, stem cell–based interventions, or pharmacological modulation of angiogenic factors, which hold promise for improving myocardial repair and function in diabetic patients suffering from ischemic heart disease (7,8).

PATHOPHYSIOLOGICAL BACKGROUND

Diabetes mellitus is characterized by chronic hyperglycemia, oxidative stress, inflammation, and endothelial dysfunction (3). These factors synergistically impair vascular homeostasis. In the myocardium, hyperglycemia leads to non-enzymatic glycation of proteins, thickening of the capillary basement membrane, and increased fibrosis. Moreover, oxidative stress results in mitochondrial dysfunction in endothelial cells and cardiomyocytes (4). Consequently, angiogenic signals, which normally ensure capillary growth and collateral formation, are markedly reduced in diabetes.

In ischemic conditions, the heart relies on angiogenesis to restore oxygen delivery. Vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1α (HIF-1α), and endothelial nitric oxide synthase (eNOS) play pivotal roles in this process (5). In diabetes, however, VEGF expression is downregulated, HIF-1α stabilization is impaired, and NO bioavailability is reduced, leading to defective vascular growth and impaired perfusion.

EXPERIMENTAL MODELS OF DIABETES AND ISCHEMIA

Several experimental models have been employed to study myocardial angiogenesis in diabetes:

- Streptozotocin (STZ)-induced diabetes – STZ selectively destroys pancreatic β-cells, leading to insulin deficiency and hyperglycemia (6).
- Alloxan-induced diabetes – another β-cell toxin used for generating experimental type 1 diabetes.
- Genetic models – db/db and Zucker diabetic fatty (ZDF) rats mimic type 2 diabetes with obesity and insulin resistance (7).
- High-fat diet (HFD) + low-dose STZ models – mimic metabolic syndrome and type 2 diabetes.
- Myocardial ischemia models – typically involve ligation of the left anterior descending (LAD) coronary artery to induce myocardial infarction (8).

These models, when combined, allow researchers to study the dual impact of diabetes and ischemia on myocardial angiogenesis.

MORPHOLOGICAL ASPECTS OF ANGIOGENESIS IN DIABETIC MYOCARDIUM

Histological and ultrastructural studies have revealed characteristic changes in diabetic myocardial angiogenesis:

1. Histological findings:
   - Hematoxylin-eosin staining demonstrates cardiomyocyte hypertrophy, disorganization, and interstitial edema.
   - Masson's trichrome and Sirius Red staining reveal increased interstitial and perivascular fibrosis (9).
   - Immunohistochemistry for CD31, von Willebrand factor (vWF), and VEGF shows decreased capillary density and reduced endothelial proliferation.
2. Ultrastructural findings:
   - Electron microscopy demonstrates swelling of endothelial mitochondria, irregular plasma membranes, thickened basement membranes, and decreased endothelial junction integrity (10).
   - Pericyte loss and rarefaction of microvessels are evident.

These morphological alterations directly correlate with impaired capillary perfusion and inadequate collateral formation in ischemic diabetic myocardium.

MOLECULAR MECHANISMS OF IMPAIRED ANGIOGENESIS

Molecular analyses provide deeper insights into the impaired angiogenic response in diabetic myocardium:

- VEGF signaling**:** VEGF expression is reduced by 30–50% in diabetic hearts, limiting endothelial proliferation and migration (11).
- HIF-1α dysregulation: Hyperglycemia impairs HIF-1α stabilization under hypoxic conditions, blunting hypoxia-driven angiogenesis.
- PI3K/Akt pathway inhibition: Insulin resistance and oxidative stress suppress PI3K/Akt signaling, which is essential for endothelial survival and angiogenesis (12).
- Endothelial nitric oxide synthase (eNOS): eNOS activity is diminished, reducing nitric oxide (NO) production and impairing vasodilation.
- Inflammatory cytokines: Elevated TNF-α and IL-6 exacerbate endothelial injury, further hindering angiogenesis (13).

These molecular disturbances explain the morphological findings of reduced capillary density and poor vascular remodeling

DISCUSSION

The combination of diabetes mellitus and myocardial ischemia leads to a profound and multifaceted impairment of angiogenesis. In non-diabetic ischemic hearts, collateral vessel formation serves as a natural compensatory mechanism to partially restore perfusion and protect viable myocardium. However, under diabetic conditions, this adaptive response is markedly compromised. Impairments in the

VEGF–HIF-1α signaling axis, together with endothelial cell dysfunction, oxidative stress, and chronic hyperglycemia, converge to suppress endothelial proliferation, migration, and tube formation (14). As a result, the ischemic myocardium in diabetes is unable to mount an effective collateralization process, thereby experiencing more extensive ischemic injury. This impaired angiogenic response has significant downstream consequences. Instead of effective neovascularization and myocardial repair, post-infarction remodeling in the diabetic heart is dominated by excessive deposition of extracellular matrix proteins, increased interstitial fibrosis, and progressive ventricular stiffening. Over time, these maladaptive processes accelerate the transition from ischemic injury to overt heart failure, with limited capacity for functional recovery.

Experimental and translational studies have highlighted several promising therapeutic strategies aimed at restoring angiogenic competence in diabetic ischemic cardiomyopathy. Among them, gene therapy with vascular endothelial growth factor (VEGF) has shown potential to enhance capillary density and improve myocardial perfusion in preclinical models. Similarly, pharmacological stabilizers of hypoxia-inducible factor-1α (HIF-1α) can amplify hypoxia-driven angiogenic signaling pathways, thereby promoting adaptive vessel growth. Nitric oxide (NO) donors and endothelial-targeted therapies may further counteract endothelial dysfunction and restore microvascular homeostasis (15).

Nevertheless, despite encouraging preclinical findings, these interventions remain largely experimental. Clinical translation is hindered by concerns related to safety, delivery methods, and long-term efficacy. Additionally, the complex metabolic environment of diabetes, characterized by persistent hyperglycemia, lipotoxicity, and systemic inflammation, may limit the effectiveness of pro-angiogenic therapies. Therefore, future research should focus on integrating molecular, cellular, and metabolic approaches—potentially combining angiogenic therapies with anti-fibrotic or anti-inflammatory agents—to achieve sustained improvements in myocardial repair and function in diabetic patients with ischemic heart disease.

CONCLUSION

Experimental models consistently demonstrate that myocardial angiogenesis is profoundly impaired under diabetic conditions, and this impairment is evident at both morphological and molecular levels. Histological examinations reveal a marked reduction in capillary density compared with non-diabetic controls, reflecting the inability of the myocardium to develop sufficient collateral circulation in response to ischemia. Furthermore, ultrastructural studies using electron microscopy have described significant endothelial alterations, including mitochondrial swelling, thickening of the basement membrane, irregularities of the plasma membrane, and loss of intercellular junctions. These structural changes not only compromise endothelial integrity but also disrupt vascular homeostasis, thereby limiting nutrient and oxygen delivery to the ischemic myocardium. In parallel, an increased degree of interstitial and perivascular fibrosis is observed, further impairing tissue perfusion and promoting maladaptive ventricular remodeling.

On a molecular level, diabetes induces dysregulation of several key angiogenic signaling pathways. Reduced expression of vascular endothelial growth factor (VEGF) and its receptors undermines the primary driver of new vessel formation. Similarly, the hypoxia-inducible factor-1α (HIF-1α) pathway, which normally upregulates angiogenic genes in response to ischemia, is suppressed in diabetic states due to hyperglycemia-induced oxidative stress and accumulation of advanced glycation end-products (AGEs). Dysregulation of the PI3K/Akt pathway further impairs endothelial cell survival, proliferation, and migration, while reduced endothelial nitric oxide synthase (eNOS) activity leads to decreased

nitric oxide bioavailability, exacerbating endothelial dysfunction and vascular rarefaction. Together, these molecular disturbances create an environment where angiogenic signaling is insufficient to meet the increased metabolic demands of ischemic myocardium. The convergence of morphological damage and molecular dysregulation underscores the critical role of angiogenesis in the pathophysiology of diabetic ischemic heart disease. These findings highlight the urgent need for therapeutic approaches that not only stimulate angiogenesis but also restore endothelial function, reduce oxidative stress, and limit fibrotic remodeling. Future strategies may involve multimodal interventions, combining gene- and cell-based therapies with pharmacological agents that target specific signaling pathways such as VEGF, HIF-1α, PI3K/Akt, and eNOS. Such integrated approaches hold promise for improving myocardial perfusion, preserving contractile function, and ultimately reducing the burden of cardiovascular complications in diabetes.

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