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Metabolic disorders in heart diseases with an inflammatory background

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This editorial refers to ‘The p65 subunit of NF- κ B binds to PGC-1 α , linking inflammation and metabolic disturbances in cardiac cells’, by D. Álvarez-Guardia *et al.*, pp. 449–458, this issue.

1. Introduction

Cardiac hypertrophy and heart failure are associated with nuclear factor- κ B (NF- κ B) activation and PPAR γ coactivator-1 α (PGC-1 α) inhibition. In this issue of *Cardiovascular Research*, the study by Álvarez-Guardia *et al.*¹ evidences a key step of cellular signalling and makes the link between these two major pathways.

2. Link between NF κ B and PGC-1 α pathways

The general term NF- κ B traditionally refers to the ubiquitous p50/p65 heterodimer. The p65 subunit provides the gene regulatory function. NF- κ B is retained in the cytoplasm complexed with I κ Bs such as I κ B α . The I κ B kinase complex (IKK), when activated by diverse upstream kinases, phosphorylates I κ Bs, inducing their degradation by the ubiquitin proteasome. Free NF- κ B heterodimers then translocate to the nucleus (Figure 1). A previous report has proposed that NF- κ B-mediated inhibition of PGC-1 α could explain the shift towards increased glycolysis under pathophysiological conditions with an inflammatory background.² The mechanistic study by Álvarez-Guardia *et al.*¹ was performed on AC16 cells resulting from the fusion of human primary ventricular cells with transformed fibroblasts and on heart extracts from mice overexpressing TNF- α . Co-immunoprecipitation experiments have allowed the authors to demonstrate that the p65 subunit of NF- κ B is constitutively bound to PGC-1 α and that NF- κ B activation increases this binding. Moreover, PGC-1 α binding to NF- κ B depends mostly on the level of p65. Finally, the interaction between p65 and PGC-1 α after NF- κ B activation results in decreased PGC-1 α expression, and as a consequence, in decreased pyruvate dehydrogenase kinase (PDK4) expression, leading in turn to an increased glucose oxidation rate (Figure 1).

3. Cardiac metabolism

In the heart, the large amounts of energy necessary to sustain contractile function and cellular homeostasis are generated primarily by mitochondrial oxidative metabolism, with a small proportion derived from glycolysis. The heart is able to use a large variety of energy substrates such as glucose, lactate, ketones and amino acids, but under normal conditions, cardiac mitochondrial ATP is mainly produced by the oxidation of fatty acids, which accounts for 60–90% of the total energy production. The key system at the border between carbohydrate and fatty acid oxidation in the mitochondrion is the pyruvate dehydrogenase complex (PDC), which catalyses the rate-limiting reaction of pyruvate decarboxylation to acetyl CoA. PDC activity is regulated by glycolysis and inhibited by fatty acid oxidation. As a result, under normal conditions, the high provision of fatty acids to the heart inhibits pyruvate decarboxylation and glucose utilization. In addition, PDC activity can be up-regulated through dephosphorylation by pyruvate dehydrogenase phosphatase, and down-regulated through phosphorylation by pyruvate dehydrogenase kinase. Therefore, the contribution of fatty acids and carbohydrates to oxidative ATP production in the heart is influenced by a number of conditions, including cardiac work, substrate and oxygen supply, but also by interactions with general intracellular signalling.

The transcriptional co-activator PGC-1 α plays a key role in the regulation of lipid and glucose oxidation in many cell types. In the myocardium, PGC-1 α activates mitochondrial biogenesis and respiration through powerful induction of nuclear respiratory factor -1 and -2 (NRF1 and NRF2) gene expression.³ PGC-1 α is highly expressed in tissues with high oxidative activity.⁴ The most illustrative example is the developing heart before the burst of mitochondrial biogenesis that precedes birth.⁵ In addition, PGC-1 α co-activates the oestrogen-related receptor- α (ERR α) transcription factors, inducing the expression of PDK4, a down-regulator of PDC.

4. Inflammation and heart failure

Since the original report of elevated levels of TNF- α in patients with chronic heart failure (CHF),⁶ there has been increasing speculation that TNF- α may contribute to the development of this pathology.^{7,8}

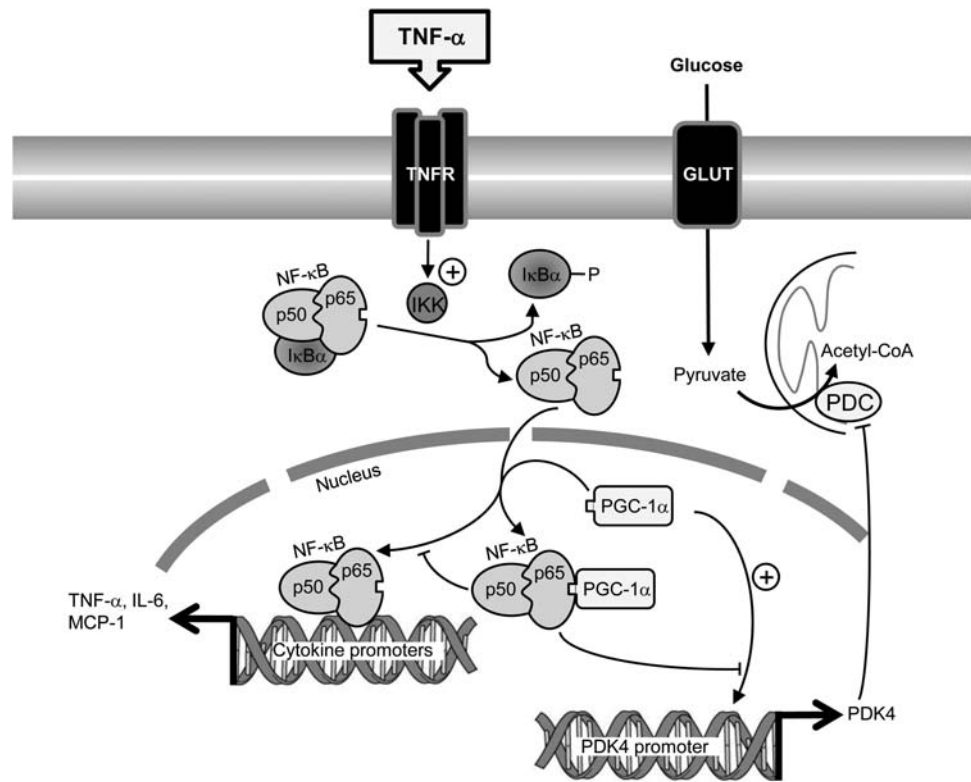


Figure 1 Proposed mechanism for TNF- α -induced increased glucose oxidation.¹ Activation of NF- κ B after TNF- α stimulation increases the binding of PGC-1 α to p65 in the nucleus. Binding of PGC-1 α to p65 reduces PDK4 expression, thereby increasing PDC activity and glucose oxidation. GLUT, glucose transporter; NF- κ B, nuclear factor κ B; I κ B, inhibitory κ B; IKK, I κ B kinase complex; PGC-1 α , PPAR γ coactivator-1 α ; PDC, pyruvate dehydrogenase complex; PDK4, pyruvate dehydrogenase kinase 4; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein 1; TNF- α , tumor necrosis factor α ; TNFR, TNF receptor.

For example, it has been shown that pathophysiologically relevant concentrations of TNF- α are sufficient to mimic certain aspects of the CHF phenotype, including left ventricular dysfunction and dilation.⁹ The pro-inflammatory cytokine TNF- α is known to modulate cardiovascular function by a variety of mechanisms. It has been shown to depress myocardial contractility by uncoupling β -adrenergic signalling, increasing cardiac nitric oxide and peroxynitrite, or altering intracellular calcium homeostasis. TNF- α may also induce structural changes in the failing myocardium, such as cardiomyocyte hypertrophy, interstitial fibrosis, and dilation. Additionally, TNF- α may promote cardiomyocyte apoptosis; it may also activate metalloproteinases and impair the expression of their inhibitors, possibly contributing to cardiac remodelling.¹⁰

In addition, several studies in patients as well as in animal models have clearly established that ATP production is reduced in the failing heart, therefore lowering the kinetics of energy utilization for cell contraction.¹¹ The energetic impairment of the failing heart includes a switch in energy substrate utilization from fatty acids to glucose, a decreased overall oxidative metabolism, a decreased mitochondrial biogenesis, an impaired transfer of ATP by the creatine kinase system, and an altered energy utilization.¹¹ The signalling pathways underlying these phenomena still remain largely unknown. Therefore, the study by Álvarez-Guardia *et al.*,¹ by demonstrating for the first time that the p65 subunit of NF- κ B in the nucleus directly represses PGC-1 α activity through physical interaction, elucidates

part of the cellular mechanisms linking pro-inflammatory states and increased glucose oxidation in myocardial cells.

5. Conclusion

The maintenance of cardiac function requires a perfectly regulated production of energy. Therefore, the control of cell metabolism in the normal heart is complex, and the interactions and links between the diverse signalling pathways are not yet fully elucidated. It is now largely accepted that dysregulation of cardiac fuel metabolism is involved in the development of numerous cardiac diseases. Álvarez-Guardia *et al.* provide improved understanding of the cellular mechanisms responsible for the shift towards glucose metabolism in pro-inflammatory conditions in the heart. A better understanding of these pathways could result in the definition of new therapeutic targets aimed at correcting metabolic disorders in pathological situations such as heart failure.

Conflict of interest: none declared.

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