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## A transcriptional coactivator as a key-partner for chronic diseases – Part I: Physiological evidence

**Two major, apparently unrelated, issues in cardiovascular research are still unsolved problems, and recent findings have suggested a common link between them, namely a regulator of the transcription process, PGC-1 $\alpha$ .**

The occurrence of such a pleiotropic partner in the medical landscape is new and important. (i) The beneficial effects of physical exercise in primary prevention of both age-related diseases and senescence are well-documented, but, for the moment, the mechanisms that link exercise and prevention are unknown.<sup>3,8</sup> (ii) Proangiogenic therapy in ischemic cardiovascular diseases is a crucial target in pharmacology, nevertheless, trials using different proangiogenic factors failed to evidence any beneficial effect in ischemic patients despite the amount of data that documented the physiological role of VEGF and many other proangiogenic factors.<sup>2</sup>

Both issues result from a complex interplay between various components of energy demand and energy supply, a central problem in biology. Exercise increases mechanical activity and energy demand, reactivates metabolic pathways, remodels muscle structure, and, by so doing allows better protection of the organism against common chronic diseases. Therapeutic angiogenesis has to respond to a deficit in oxygen delivery, not only by stimulating vessel growth, but also by stimulating oxidative metabolism. Then, in both cases, biological regulation has to be located at a highly integrated level of regulation, upstream of the classical metabolic pathways, such as glycolysis, fatty acid metabolism, and protein synthesis.<sup>4</sup>

Such a level is well-known in basic biology, and is located in the central cell machinery, ie, nuclei, to explain why, in these conditions, as in many others<sup>3</sup> the cell response does not concern, as previously thought, a small group of genes or proteins, but the coordinated and modular expression of clusters of genes.<sup>4</sup> Nuclear receptors are good candidates and could be the appropriate level at which multiple nutritional or physiological stimuli have been reactivated.<sup>1,3</sup> Several observations emerging

over the last years have implicated the PPAR $\gamma$  transcriptional coactivator-1, PGC-1, family as key mediators for physiological energy control and structural adaptation. The family includes many inducible members, but PGC-1 $\alpha$  seems to play a central role.<sup>3</sup> The present series aims to delineate this new research area.

In skeletal muscle, transgenic technology has unambiguously demonstrated that endurance training induced fiber-type switching towards a more oxidative type I and type IIA muscle fiber,<sup>7</sup> and that such a shift was linked to an increased PGC-1 $\alpha$  expression.<sup>3,6</sup> Then, the activation of PGC1- $\alpha$  controls muscle fuel selection by increasing fatty acid oxidation and mitochondria synthesis, and shutting down glucose oxidation and activating glucose uptake (through the expression of a glucose transporter) which in turn could serve to replenish glycogen stores to prepare for the next exercise episodes. There is much evidence that the signal which, indirectly, activates PGC-1 $\alpha$  expression (and several other transcription factors) during physical activity is the calcium released from sarcoplasmic reticulum, which in turn activates a rather complex chain of intermediary products, including the calcineurin pathways.

**In the heart, PGC-1 $\alpha$  plays a comparable key role, and is activated soon after birth when mitochondria become the main energy source, but is also stimulated by fasting which enhances the reliance of the myocardium on fatty acid production.<sup>3</sup> The assumption is still valid in chronic mechanical cardiac overload. In this condition, the well-documented metabolic shift towards a more anaerobic metabolism is indeed accompanied by a pronounced downregulation of cardiac PGC-1 $\alpha$  level.<sup>5</sup>**

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