

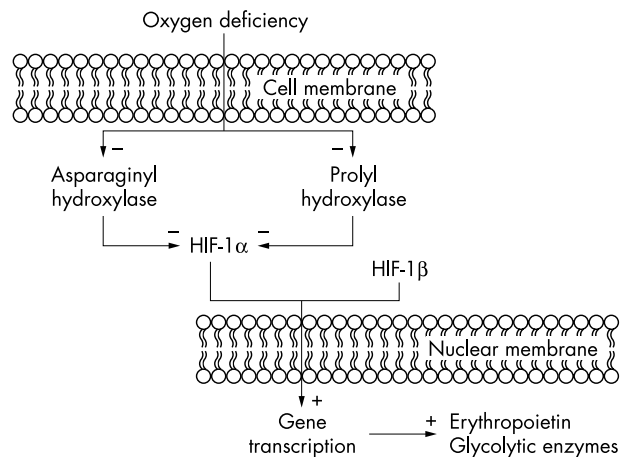
## OCCASIONAL PIECE.....

## Gene manipulation and improvement of athletic performances: new strategies in blood doping

**A**erobic athletic performances are greatly improved by optimisation of mechanisms of oxygen transport and delivery to peripheral tissues and muscles. There are both lawful and banned methods to achieve better muscular oxygenation; of these, the administration of erythropoiesis stimulating molecules, namely human recombinant erythropoietin (rHuEpo) or NESP, has been widely used by endurance athletes since the early 1990s.<sup>1</sup> However, the introduction of a reliable laboratory test to detect blood doping with rHuEpo or derivatives has forced athletes to rely on alternative techniques, including blood and gene doping.<sup>1,2</sup>

The recent discovery of a novel family of proteins called hypoxia inducible factors (HIFs) has increased our understanding of the intricate mechanisms of the response to hypoxia, as occurs in tissues that in some circumstances have to deal with increased oxygen demand, such as hard working muscles. HIFs are transcription factors which modulate the activity of a variety of genes in conditions of relative low oxygen availability. In low oxygen conditions, the activity of two intracellular enzymes that promote the degradation of HIF-1 $\alpha$  (asparaginyl hydroxylase and prolyl hydroxylase) is inhibited.<sup>3</sup> Therefore, HIF-1 $\alpha$  binds to HIF-1 $\beta$ , crosses the nuclear membrane, and binds to intranuclear proteins, promoting gene transcription (fig 1). The genes controlled by the HIFs include those coding for proteins that stimulate red cell production (Epo), as well as those encoding glycolytic enzymes which produce additional energy in conditions of relative oxygen deficiency, both of which are pivotal mechanisms in the attempt to achieve improved aerobic athletic performances. Researchers have recently developed novel agents that target HIFs. The biochemical or genetic manipulation of HIFs is a promising therapeutic approach for pathological conditions characterised by alteration of oxygen metabolism, such as cancer, inflammation, heart attack, and stroke, but may also represent potential targets for gene doping. Unfortunately, the manipulation of HIFs may have detrimental consequences: in addition to their beneficial effects on blood oxygenation, HIFs stimulate genes that encode angiogenic molecules and proteins involved in cell growth, division, survival, and mortality, which may finally promote cancer growth and spread.<sup>3</sup>

In conclusion, the recent discovery that oxygen deficiency stimulates Epo production through the HIF pathway may represent an attractive approach for increasing red blood cell mass that is virtually unidentifiable by current antidoping



**Figure 1** Regulation of erythropoietin and glycolytic enzyme production during hypoxia.

procedures, without resorting to the administration of exogenous erythropoietic stimulating substances.<sup>4</sup> Although there is currently no evidence for gene doping, we suggest that novel drugs that modulate HIF expression and metabolism might be recognised and soon included in antidoping panels.

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