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Thin air - thick science

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Journal club

THIN AIR — THICK SCIENCE

While preparing a physiology lecture about high-altitude adaptation, I recently stumbled across an old textbook illustration showing how HIF-1 binds to the 3' enhancer of the gene encoding erythropoietin (EPO) to increase oxygen transport capacity of the blood. In retrospect, part of this illustration is wrong. It is actually HIF-2 and not HIF-1 that regulates EPO and the 3' enhancer is not required for EPO induction in vivo in the kidney. Nevertheless, this cartoon reminded me of a seminal study by Semenza and Wang, which paved the way to last year's Noble Prize in Physiology or Medicine.

In this study, the authors used a large panel of radioactively labelled short oligonucleotides to identify proteins interacting with a 50 bp 3' region of the *EPO* gene in hepatoma cells. Strikingly, they could observe a single small band in their autoradiographs only when cells were cultured under low oxygen. This band corresponded to a protein they subsequently named 'hypoxia-inducible factor-1'. Apparently, they anticipated that there will be an entire family of HIFs. Now we know that HIFs function as heterodimers between three distinct α subunits and a common β subunit, but only the α subunits respond to oxygen levels.

Since then, whoever exposed whatever kind of cells to hypoxic conditions noted a stabilization of HIF α proteins and an induction of hundreds of target genes. This led to the conclusion that HIFs are ubiquitously expressed and that their target genes cross-talk with virtually all cellular pathways. However, what is still puzzling is the differential gene regulation mediated by the two key factors, HIF-1 and HIF-2, and their distinct physiological functions and roles in disease. How does a common oxygen sensing and signalling pathway lead to a specific and only partially overlapping pattern of HIF-1 and HIF-2 target genes?

With the availability of new technologies, Smythies et al. could

recently map the genome-wide interaction of HIF-1 and HIF-2 with chromatin and provide an unexpected answer to this question: they observed that HIF-1 and HIF-2 preferentially bind proximal and distal, respectively, to the promoter regions of the corresponding target genes. There is no simple explanation for this robust site-selectivity — the recognition sequence is identical among the approx. 1,000 HIF-1 and HIF-2 DNA interaction sites, and it is the same sequence that Semenza and Wang identified more than a quarter of a century ago. With the first HIF α stabilizing and EPO inducing drugs currently entering the market for the treatment of patients with chronic kidney disease, the question of how to selectively target HIF-1 α and HIF-2 α became of even greater importance.

Surprisingly, despite the overwhelming evidence for the role of oxygen in cellular function, the importance of controlling oxygen levels is still mostly ignored in cell culture experiments. This common habit is likely to contribute to the low reproducibility of research results that we face today.

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The author declares no competing interests.

ORIGINAL ARTICLES Semenza, G. L. and Wang, G. L. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. *Mol. Cell Biol.* **12** 5547–5554 (1992) | Smythies, J. A. et al. Inherent DNA-binding specificities of the HIF-1 α and HIF-2 α transcription factors in chromatin. *EMBO Rep.* **20**, e46401 (2019)