HYPOTHESIS

Gradients of $O_2$ control skeletal development and homeostasis by regulating the HIF pathway
HIF-1α (Hypoxia Inducible Factor)

- PAS (PER-ARNT-SIM) subfamily of bHLH transcription factors
- heterodimer HIF-1α/ARNT; HIF-1α, the hypoxia-responsive component of the complex
- ubiquitously expressed and highly unstable
- another member in the family, HIF-2α
HIF-1α: A KEY FACTOR IN CELLULAR ADAPTATION TO HYPOXIA
HIF-1α: A KEY MEDIATOR OF CELLULAR ADAPTATION TO HYPOXIA

In normoxia, HIF-1α protein is rapidly degraded by the proteasome.

Modified from Nature Review Rheumatology 2012; 8:358-366
HIFs: A HOMEOSTATIC RESPONSE TO KEEP HYPOXIA “IN CHECK”

- **O₂ CONSUMPTION**
  - **MITOCHONDRIAL METABOLISM**
  - **CELL NUMBER /MATRIX RATIO**

- **BLOOD VESSELS**
  - **O₂ AVAILABILITY**

- **REDox STRESS**
  - **RED BLOOD CELLS**
  - **ROS METABOLISM**
HYPOTHESIS

The complex actions of HIFs on O$_2$ homeostasis are exploited to modulate development and homeostasis of skeletal elements.
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