# Evolution of multicellularity relies on low oxygen

or Cancer research encourages explorations of hypoxic conditions as a necessity for multicellularity
or How animals solved the challenge of life in the oxic setting

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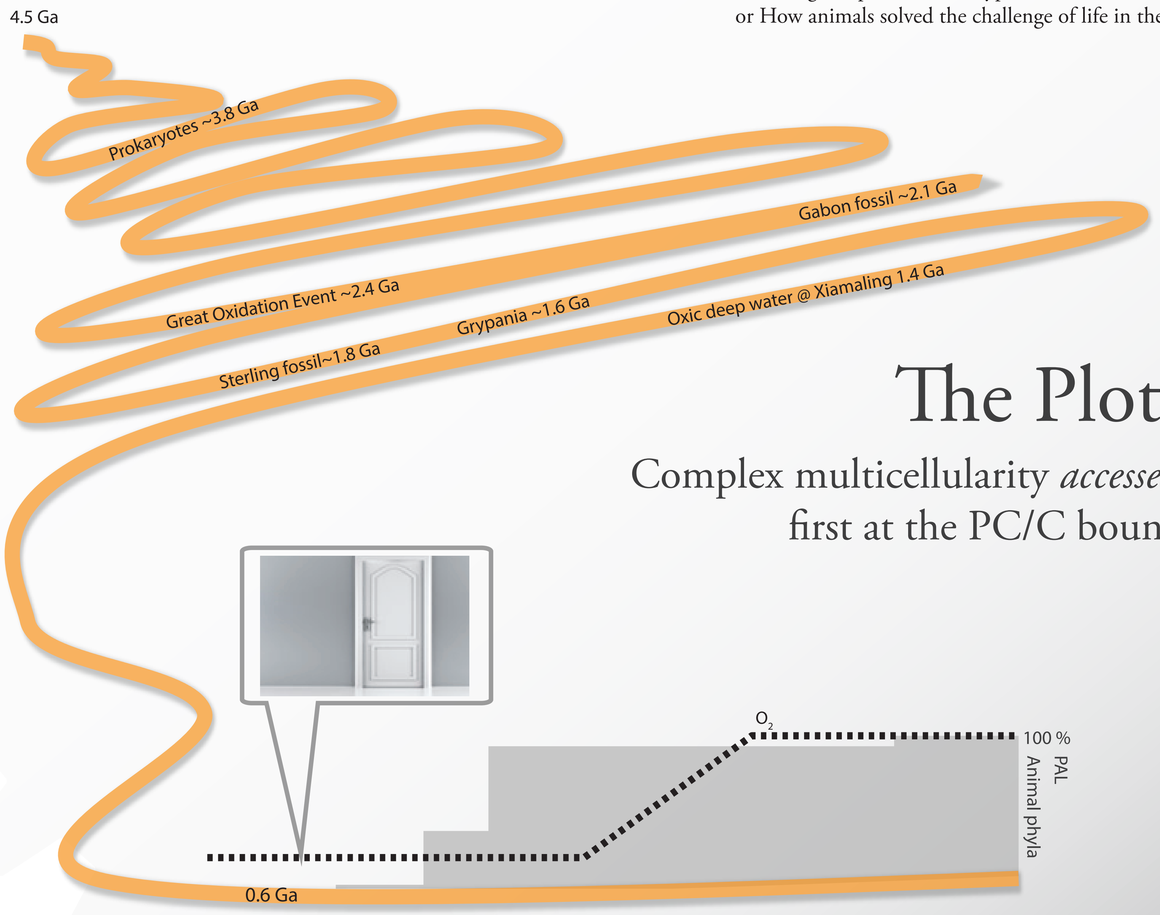
TUMOR BIOLOGY

GEOBIOLOGY

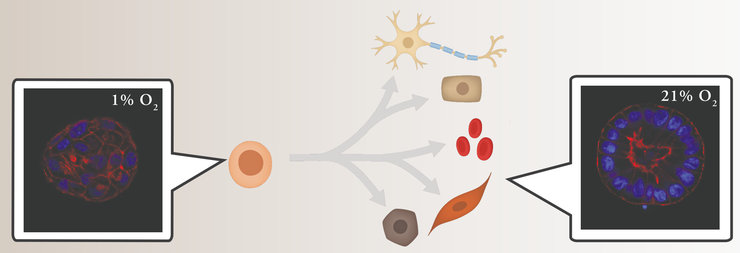
## The Plot

Complex multicellularity *accessed* the oxic niche first at the PC/C boundary...



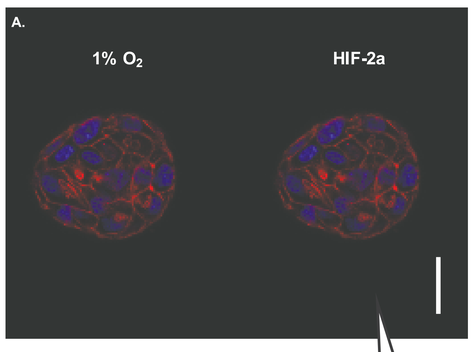

## A Clue

Animals possess unique biological tools to build tissue *despite* oxic conditions.

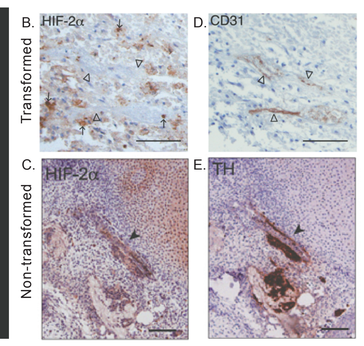



- Animal life & evolution requires continuous tissue renewal.
- Tissue renewal requires stem cells.
- Stem cells require hypoxia (<1-3% $O_2$) [1, 2].
- Animals can induce hypoxic responses and cell stemness despite oxygen [3].
- Cell stemness is yet mainly studied in tumors.

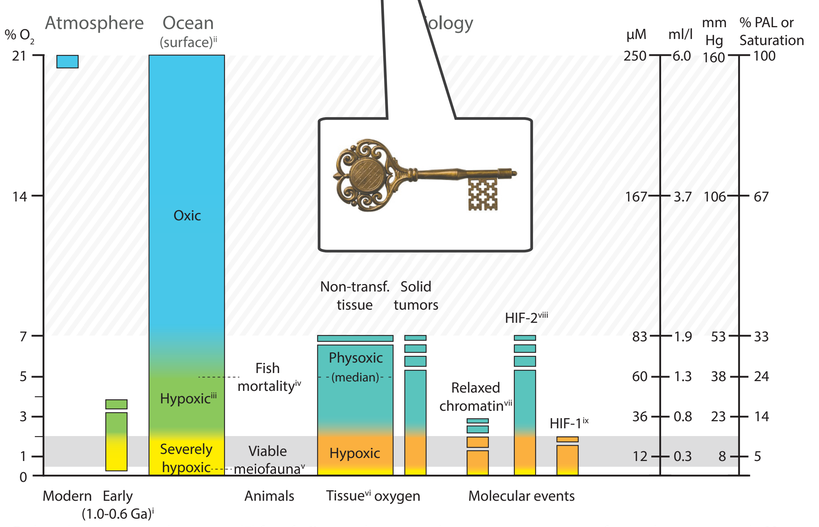
## Animal-specific keys for building tissue



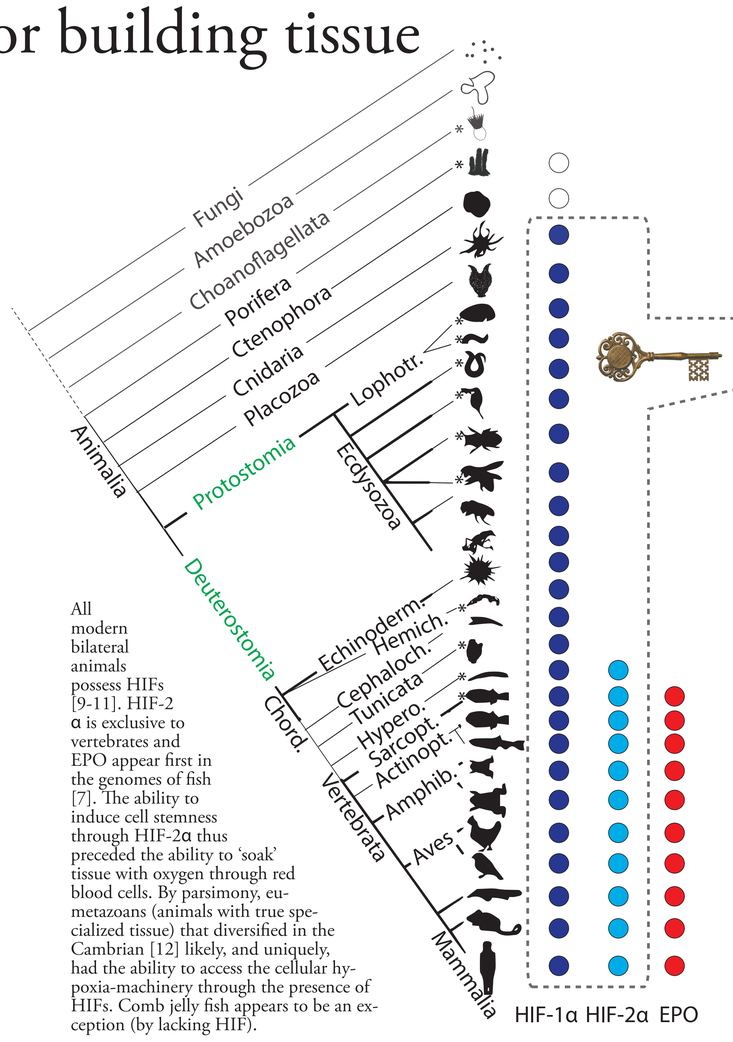

HIF-2α protein appears to facilitate the activation of pathways promoting (A) stem cell-like features [4], called the pseudohypoxic phenotype [3]. Scale bar 20 µm. Modified from [4].




HIF-2α is present in vascularized both in (B) tumor tissue (neuroblastoma) [5] and (C) during normal tissue development (human) [6], where cell immaturity (high stemness) is indicated by how (D) endothelian cells are CD31-positive or (E) sympathetic ganglia are TH-positive. Scale bar: 200 µm.

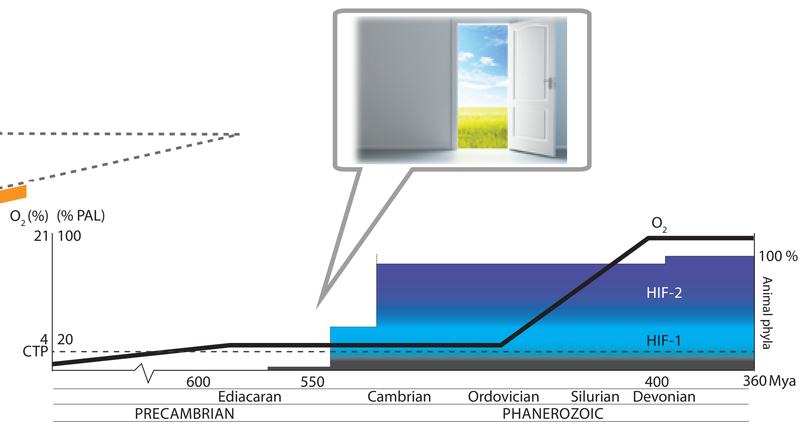



Biological action occurs at hypoxia, see [7] for refs. Compared to estimated maximum concentrations of atmospheric oxygen in the Neoproterozoic/Paleozoic [8], the function of HIF-2α protein spans into higher O2 concentrations. The HIF system can be considered an adaption to niches with high (>1-2%) and flucutating oxygen concentrations [7].

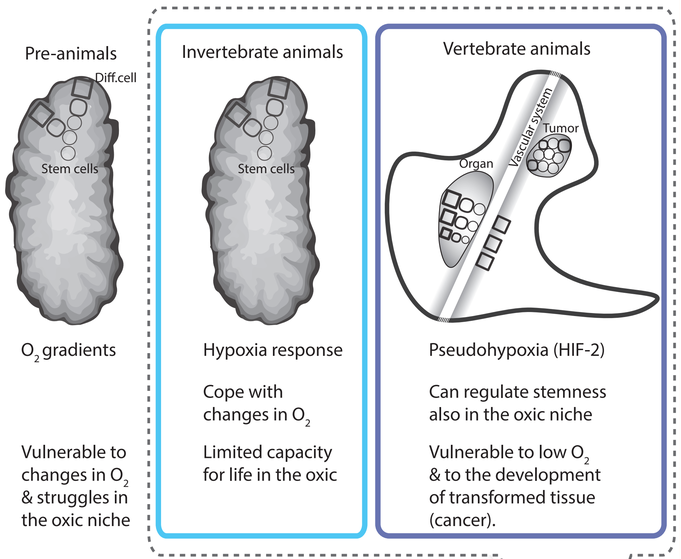



All modern bilateral animals possess HIFs [9-11]. HIF-2α is exclusive to vertebrates and EPO appear first in the genomes of fish [7]. The ability to induce cell stemness through HIF-2α thus preceded the ability to 'soak' tissue with oxygen through red blood cells. By parsimony, eumetazoans (animals with true specialized tissue) that diversified in the Cambrian [12] likely, and uniquely, had the ability to access the cellular hypoxia-machinery through the presence of HIFs. Comb jelly fish appears to be an exception (by lacking HIF).

## The model




We propose that an evolution of stemness control through HIFs allowed the generation and re-generation of complex tissue in conditions with oxygen concentrations >1-3 % O2 [7]. Eumetazoa first and most efficiently gained access to the oxic niche. This evolution of stemness control occurred in at least two steps, with each level defined by how its control of cell stemness is adjoined by the abilities and vulnerabilities within complex tissues.




*If* animals diversified as a result of improved stemness control...

...then, transient hypoxia and pseudohypoxia remain *key* for tissue development & for animal evolution.

## Testable implications

**Geology:** Were early and complex multicellular life forms confined to stable environments?

**Biology:** Tissue oxygen tension – and HIF expression – is measured within the chick embryo at different developmental stages, particularly during the development of the sympathetic nervous system.

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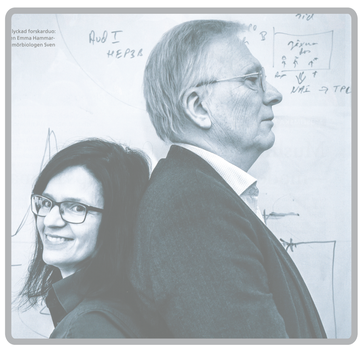

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