In God we trust

mTOR and hypoxia signaling interactions

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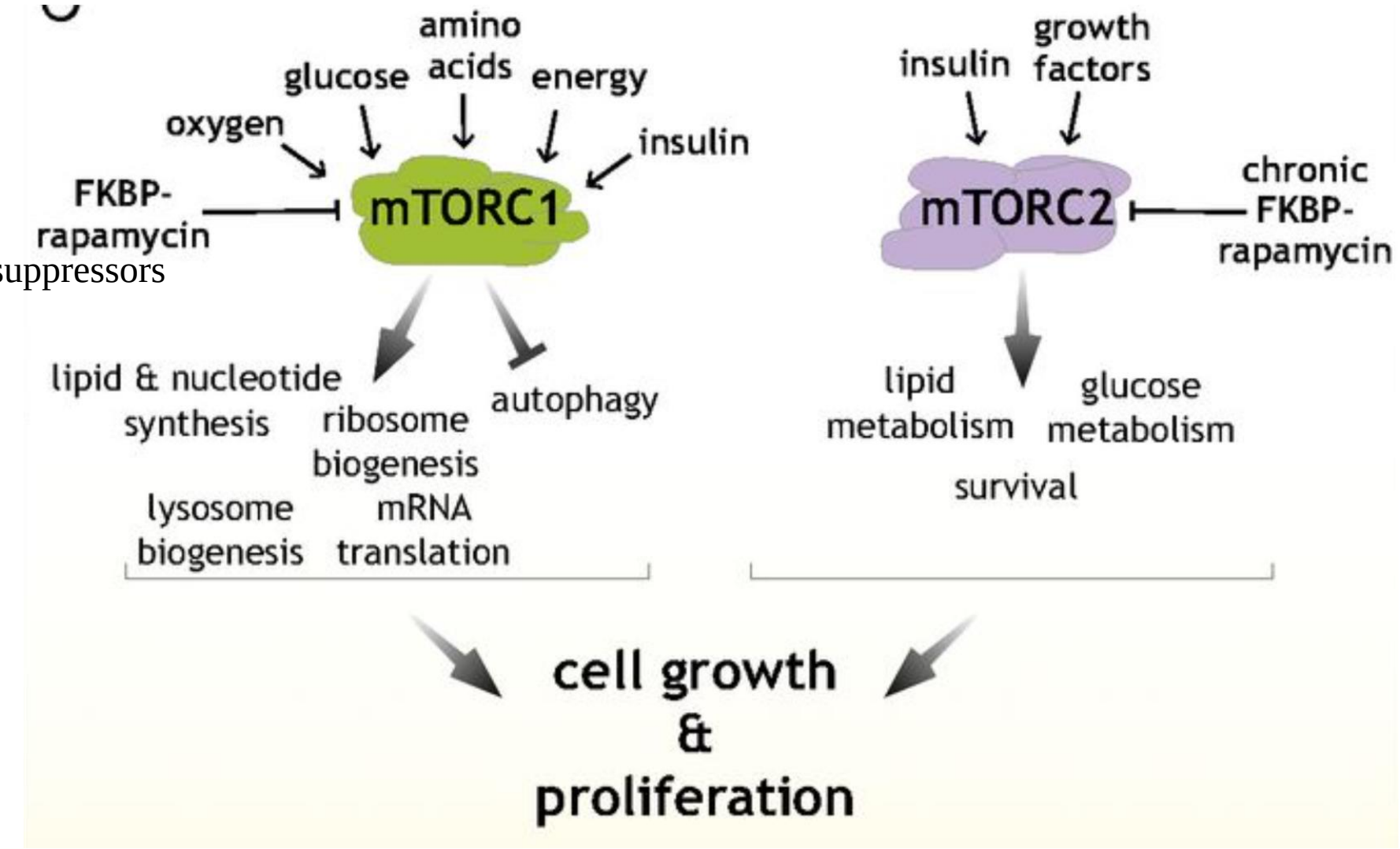
The mammalian target of rapamycin (mTOR)

- ✓mTOR is a serine/threonine kinase that is associated with other factors to form 2 complexes (mTORC1 and mTORC2).

- ✓ mTOR regulates cap-dependent translation, transcription, cell cycle progression, and survival.

Tumor suppressors
Stresses



mTOR activity is affected by different factors

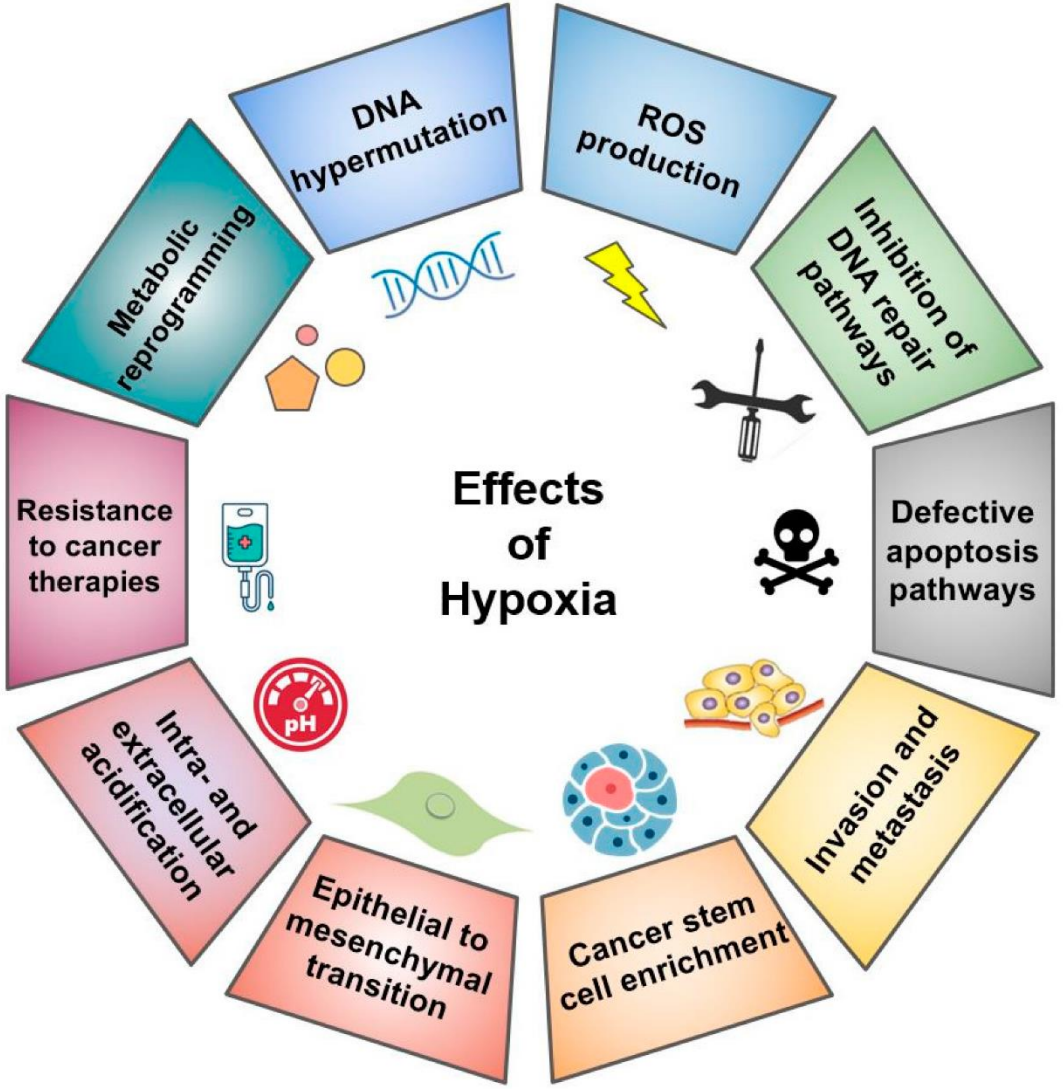
mTORC1 activity is sensitive to O2 deprivation

- Given its role in protein synthesis and cell growth under nutrient- and energy-replete conditions, it is perhaps not surprising that:
  mTORC1 activity is also sensitive to O2 deprivation.

- In fact, hypoxia inhibits mTORC1 through multiple pathways, particularly in concert with other stresses or when hypoxic conditions are chronic.

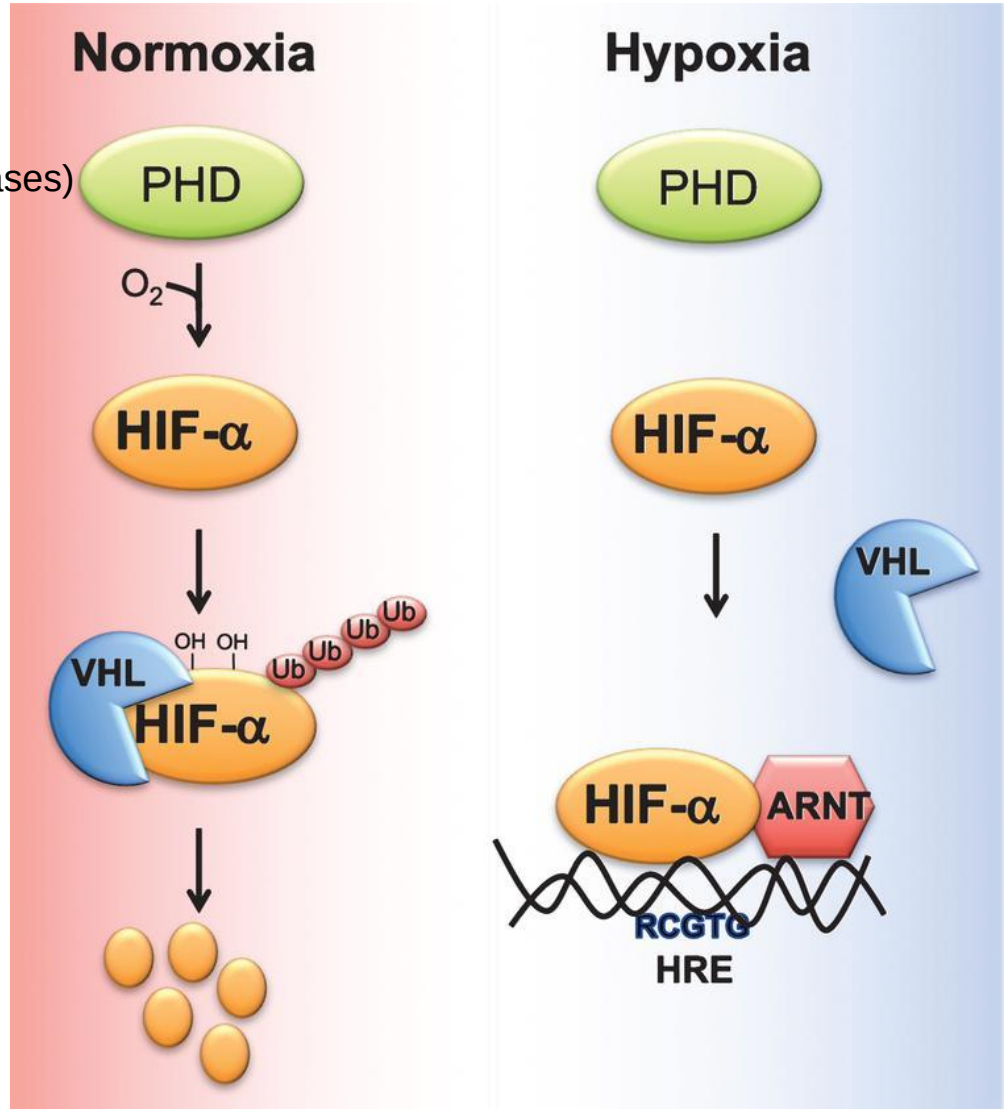
Hypoxia

- Responses to hypoxia are orchestrated in part through activation of the hypoxia-inducible factor family of transcription factors (HIFs)
- HIF is a master regulator of hypoxic adaptation
- HIF is strongly implicated in tumor growth.
- HIF is translationally regulated by mTOR.



1. HIF

(prolyl hydroxylases)

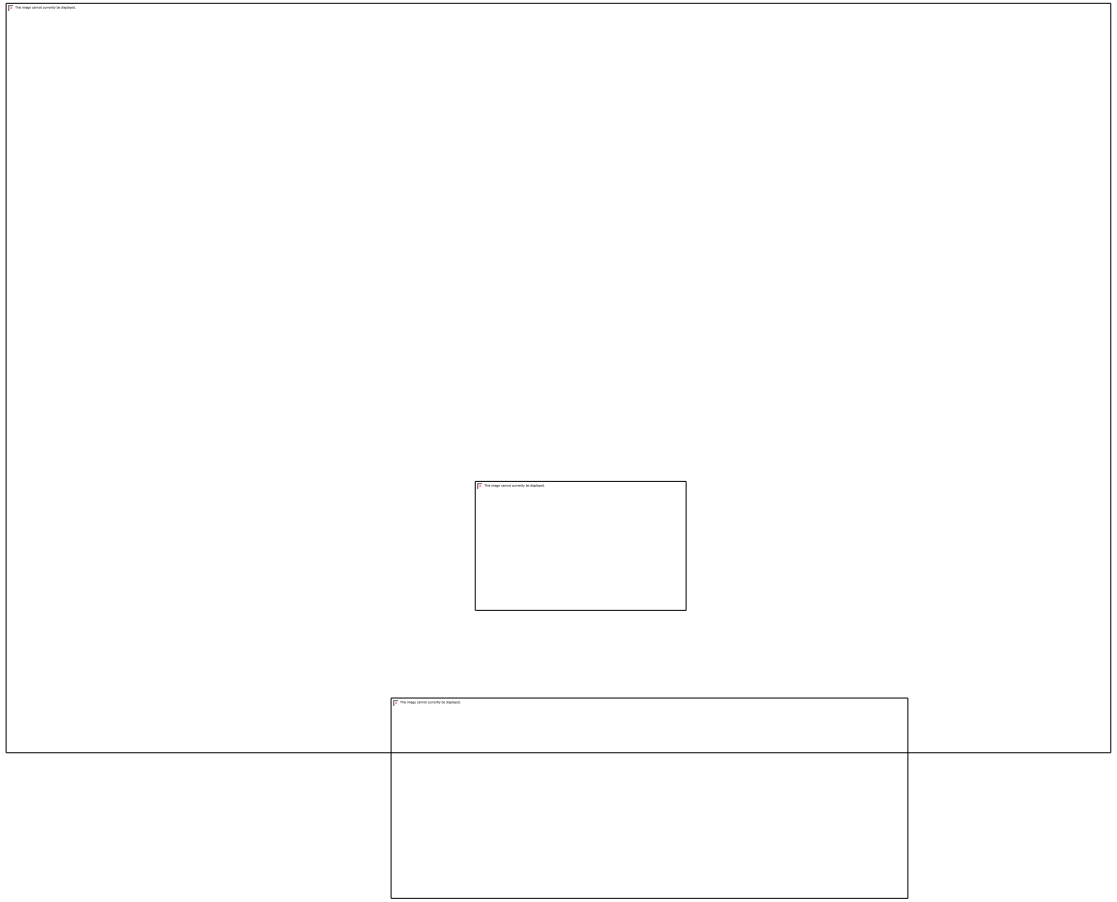


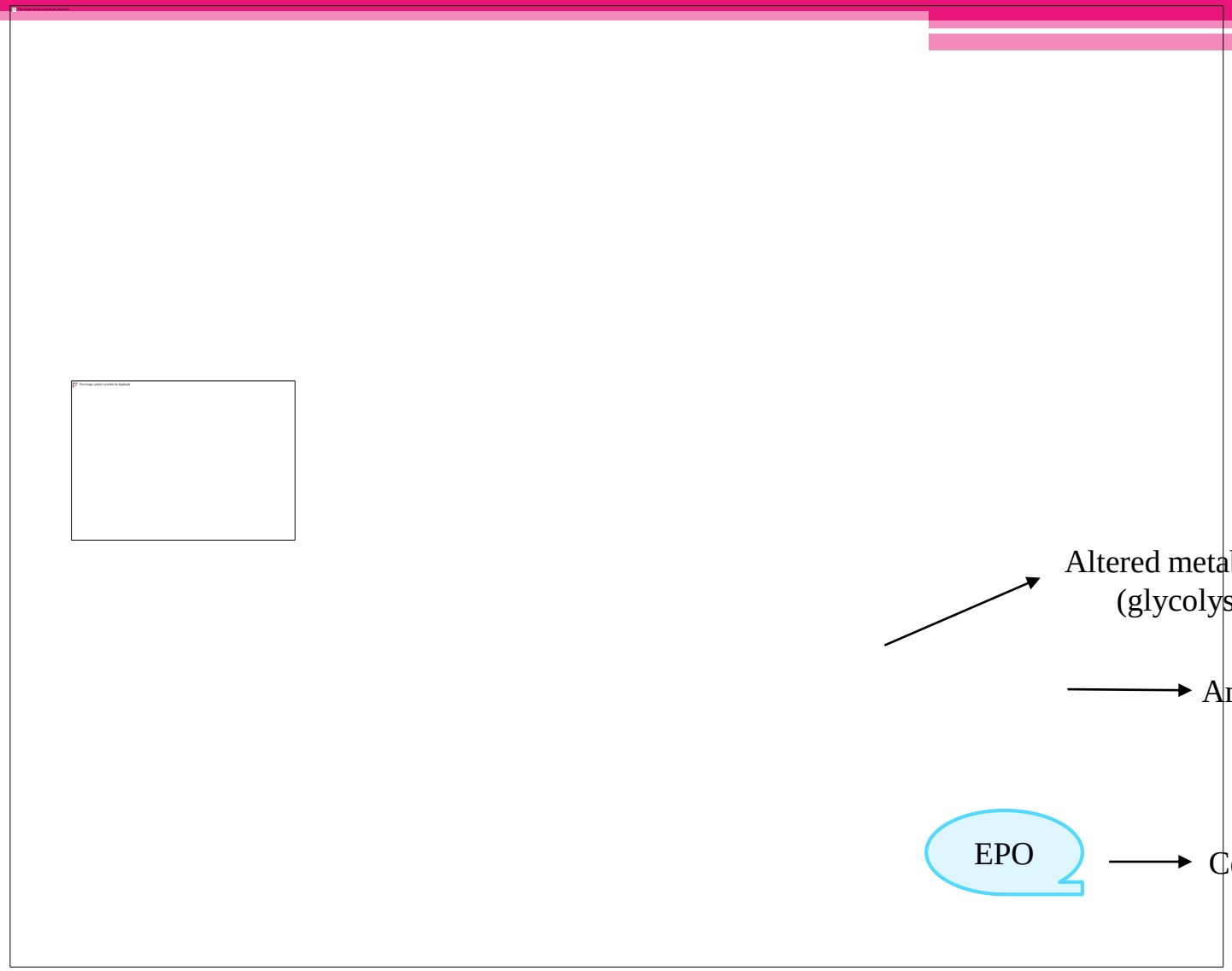
Other hypoxia signaling pathways

Two additional O_2-sensitive signalling pathways have also been implicated:

- ✓1. HIF
- ✓2. signalling through the mTOR kinase
- ✓3. signalling through activation of the unfolded protein response (UPR)

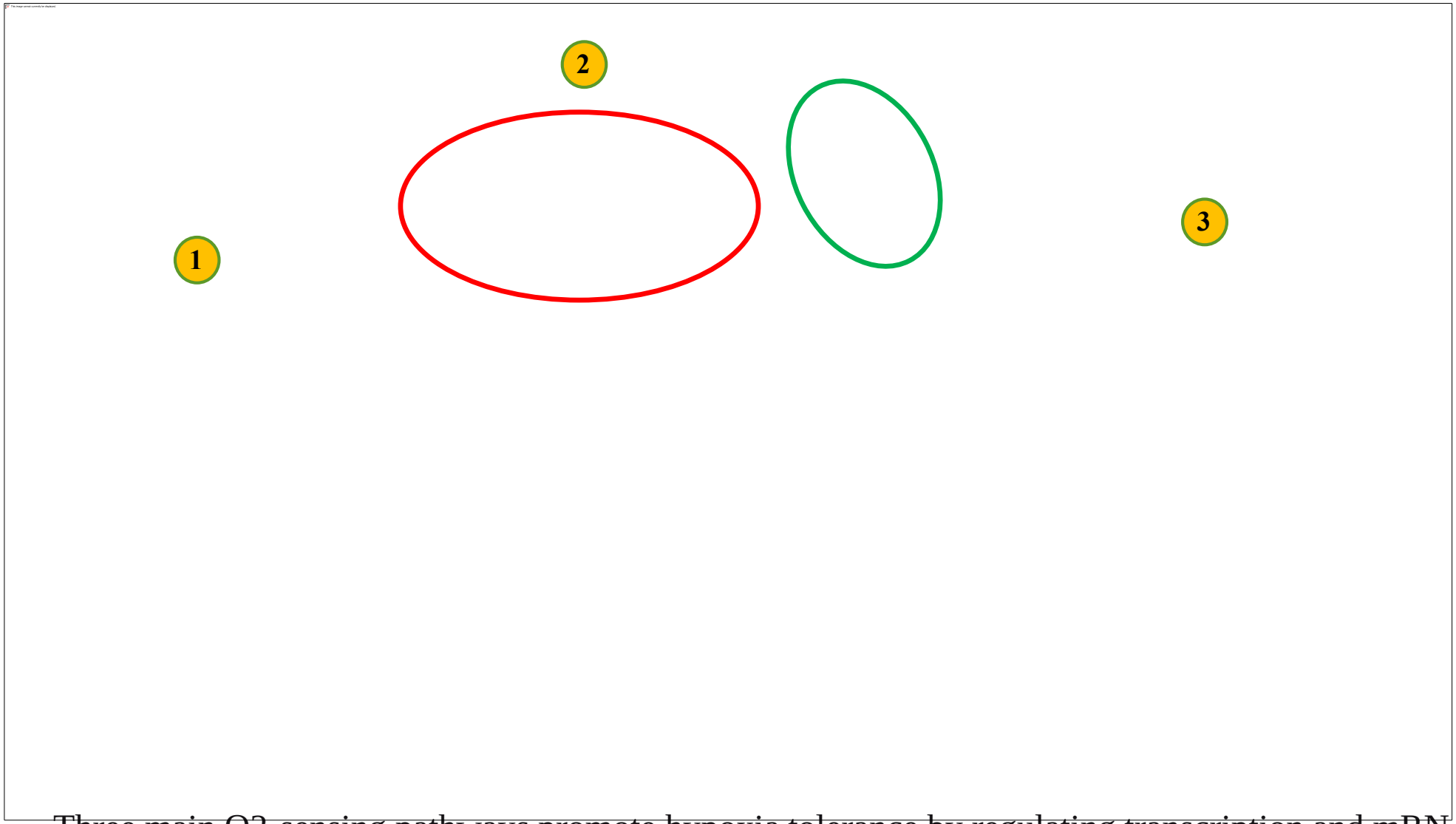
2. mTOR controls responses to hypoxic stress





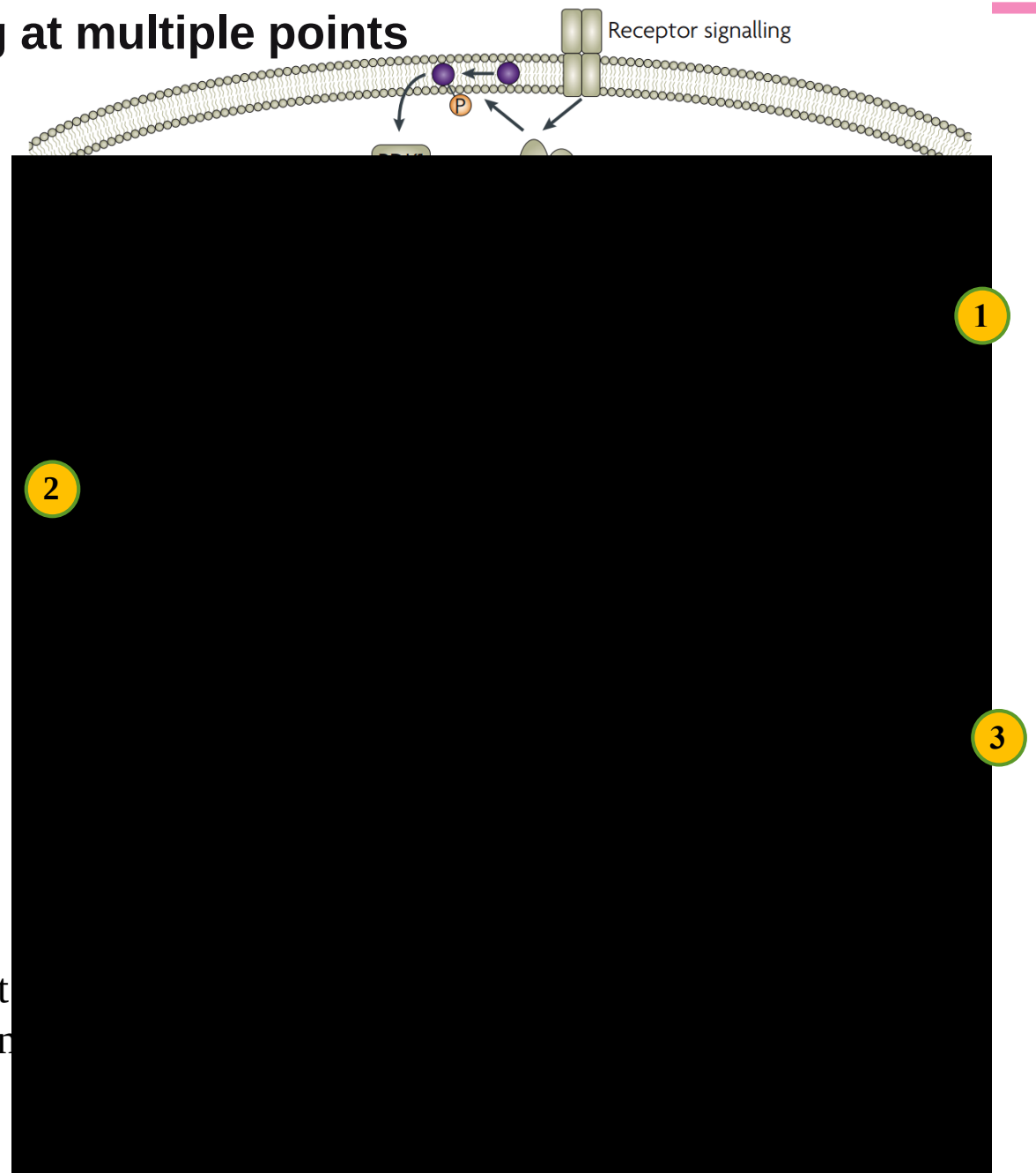
- Accumulated HIF-1 translocate to the nucleus, and binds to the hypoxia-response element (HRE) then regulates the expression of genes involved in tissue survival (angiogenic, c, erythropoietin and inducible nitric-oxide synthase) in hypoxia

Cellular O2-sensing pathways



Three main O2-sensing pathways promote hypoxia tolerance by regulating transcription and mRNA translation.

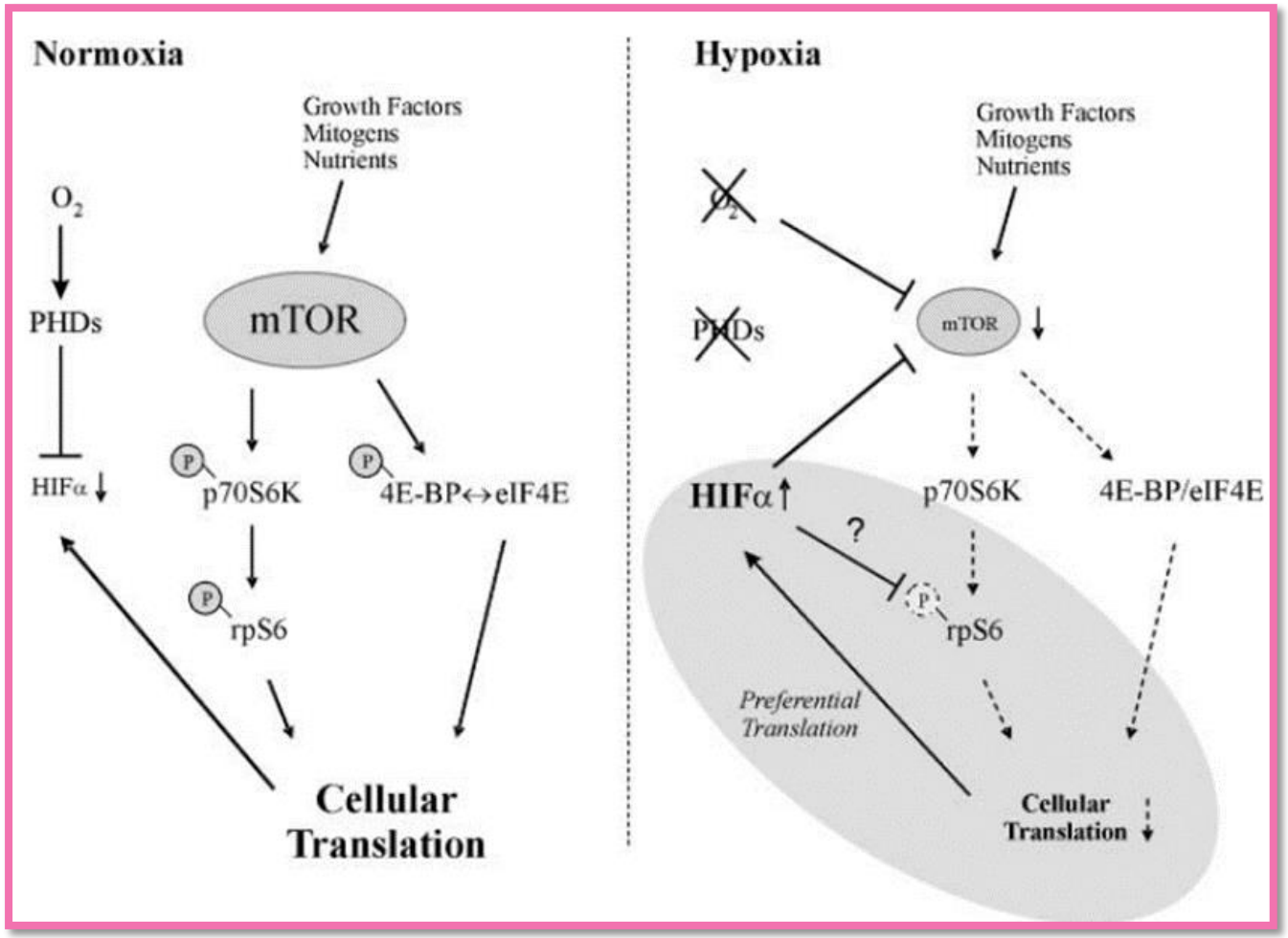
Hypoxia influences mTOR signalling at multiple points



Hypoxia is able to activate TSC1/2 to inhibit
through the Redd1 (transcriptional regulation
response 1) gene

Model of the complex interactions between HIF and mTOR in dependency of oxygen availability

- Under hypoxia, mTOR is potently inactivated, which leads to diminished cellular translation and rapid hypophosphorylation of p70S6K, which is in part a function of HIF itself.
- The rpS6 is hypophosphorylated in a much slower manner, which may enable a certain degree of preferential translation under hypoxia.
- However, prolonged hypoxia also inactivates rpS6, probably in part driven by HIF and representing a negative feedback loop.



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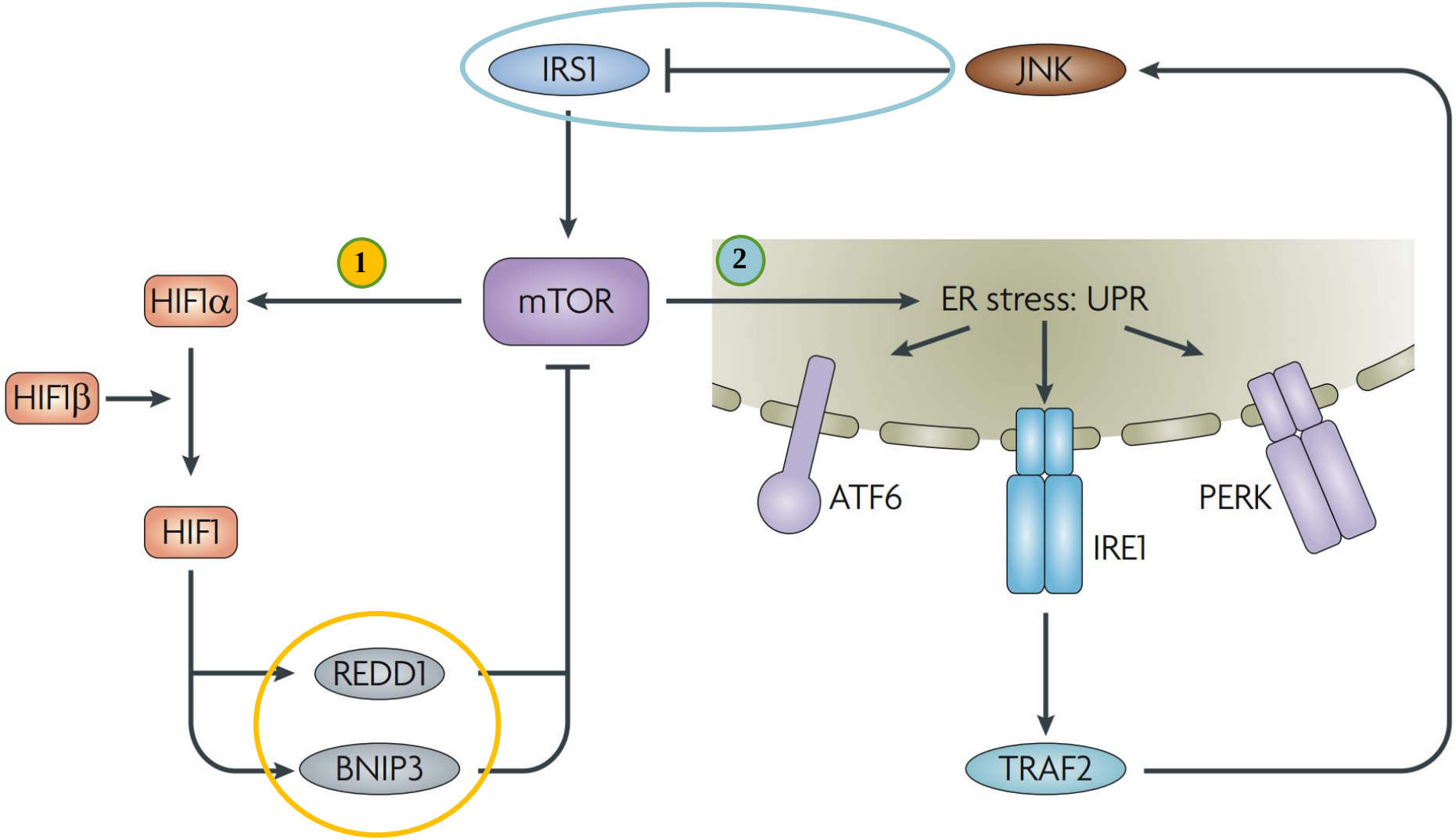
Negative feedback loops from HIF1 and unfolded protein response (UPR) to mTOR



mTOR, hypoxia, and cancer

- Hypoxia occurs in the majority of tumours, promoting angiogenesis, metastasis and resistance to therapy.
- mTOR has the potential of stimulating HIF in a large panel of cells
- mTOR inhibition leads to profound decrease of HIF α protein in the majority of primary and cancer cells studied.
- However, specific influences, such as cell type, amount of serum, and degree of hypoxia, considerably interfere with this response.
- Under severe hypoxia, HIF seems to be operating independently of mTOR.

stimulation of HIFα by mTOR may only be relevant under mild hypoxia or even normoxia.

Home messages

- ✓ Under hypoxia, mTOR is inactivated, which is believed to be part of the program of the cell to maintain energy homeostasis.
- ✓ HIF is the master regulator of hypoxic adaptation and itself strongly implicated in tumor growth.
- ✓ HIF is translationally regulated by mTOR.
- ✓ evidence suggests that **HIF-, mTOR- and UPR-dependent responses to hypoxia** act in an integrated way, influencing each other and common downstream pathways that affect gene expression, metabolism, cell survival, tumorigenesis and tumour growth.
- ✓ The hypoxic microenvironment reduces tumor cells resistant to mTOR inhibition, at least regarding hypoxic gene activation.


Thank you for your attentive listening