−1.0 −0.5 0.0 0.5 1.0

HIF-1 SIGNALING PATHWAY

IL-6 → IL-6R → STAT3

DNA

LPS
TLR4 → NF-κB

HIF-1α mRNA

IFN-γ → IFN-γR

MAPK signaling pathway

E3 ubiquitin ligase complex

TIMP-1 → Matrix and barrier functions

CD18 → Inflammation

GF → RTK → MEK → ERK → MNK

VHL | Rbx1
ElonginC | CUL2
ElonginB

Ubiquitin mediated proteolysis

Increase oxygen delivery

EPO → Erythropoiesis

Translation

PI3K

4E-BP1 → eIF4E

TF | TFRC → Iron metabolism

AKT → mTOR → p70S6K → rpS6

+u

Degradation

VEGF | Flt-1

HIF-1α

EGF | PAI-1 → Angiogenesis

mTOR signaling pathway

PHD

2-OG

ANGPT | Tie-2

PI3K-Akt signaling pathway

PKC

NO

Normoxia

Asc

O2 Fe²⁺

TIMP-1

VEGF signaling pathway

Continuous hypoxia

HIF-1β

DNA

DAG IP3

Hypoxia

EDN1 | iNOS

CamK → p300/CBP

PLCγ

Ca²⁺

eNOS | HMOX1 → Vascular tone

Calcium signaling pathway

ANP

Intermittent hypoxia

NOX

ROS

Reduce oxygen consumption

Glut1 → Promote anaerobic metabolism

PDK-1 → Inhibits TCA cycle metabolism

PDK-1

+p

HK | PFKL

PDH

GAPDH | ALDOA

Glucose → Glut → Pyruvate → Acetyl-CoA → Citrate cycle (TCA cycle) → ATP

ENO1 | PGK1

Promote anaerobic metabolism

PFK2

Mitochondrion

O2

LDHA

LDHA

Lactate

Bcl-2 → Regulate proliferation and apoptosis

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04066 8/5/21
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