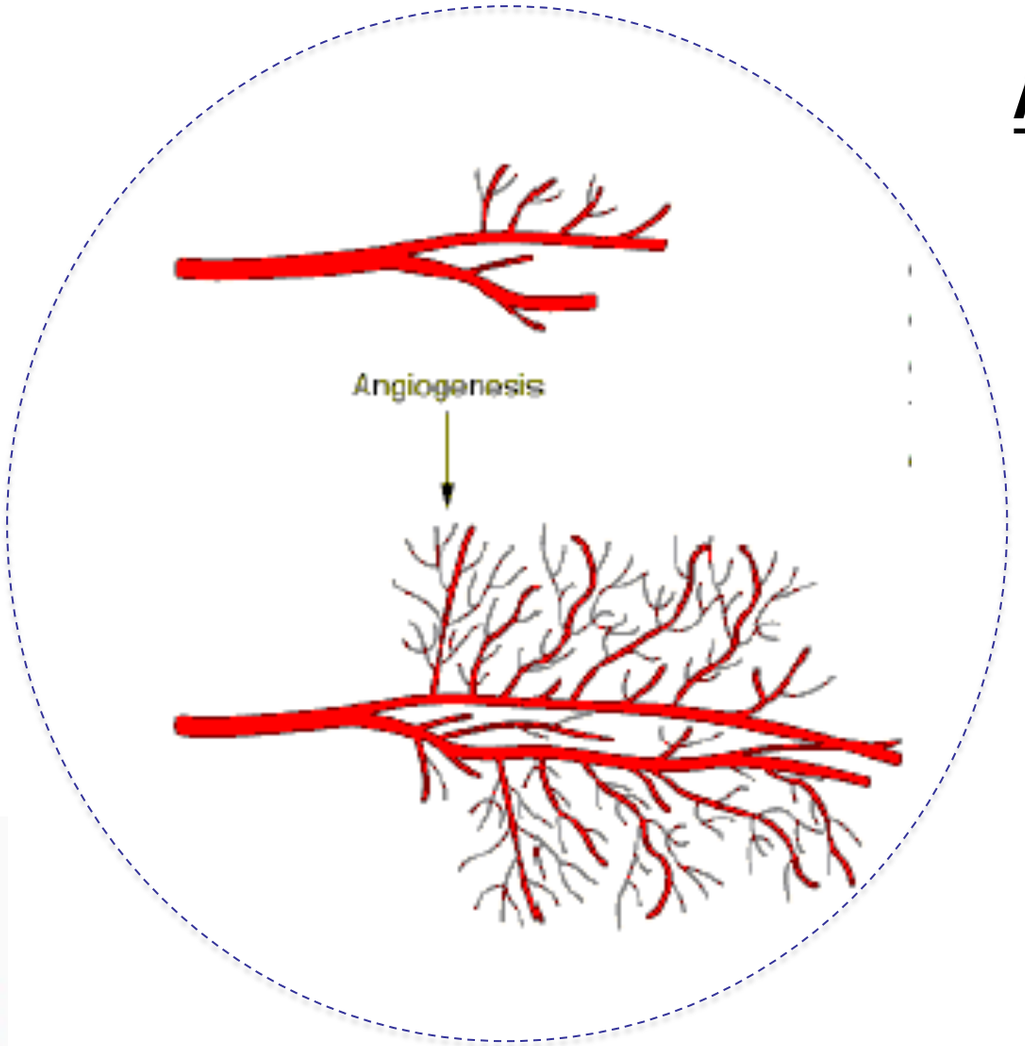
METABOLIC CONTROL OF TRANSLATION IN ANGIOGENESIS

ENDOTHELIAL METABOLISM: an hallmark of physiological, pathological and therapeutic angiogenesis

Signaling

Migration

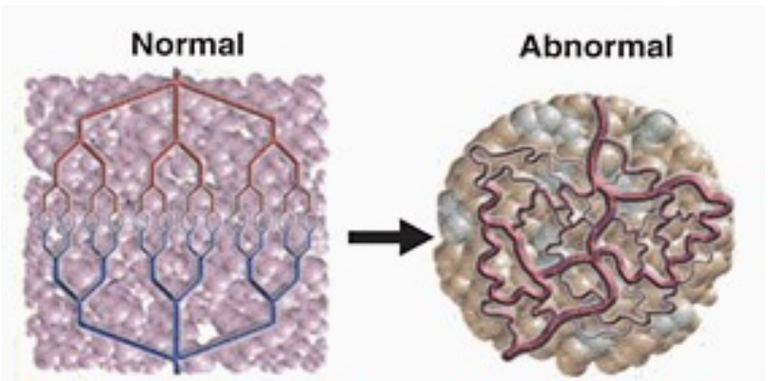
ECM

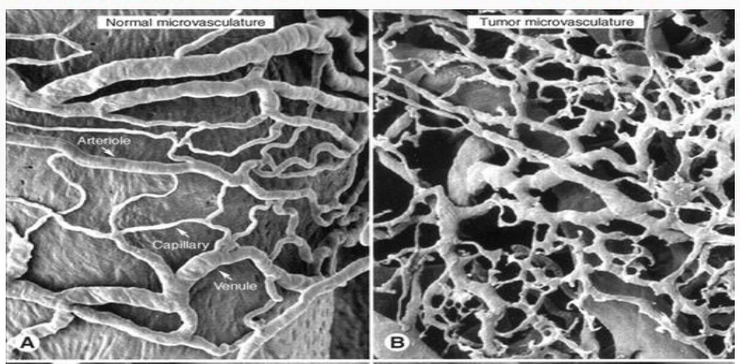


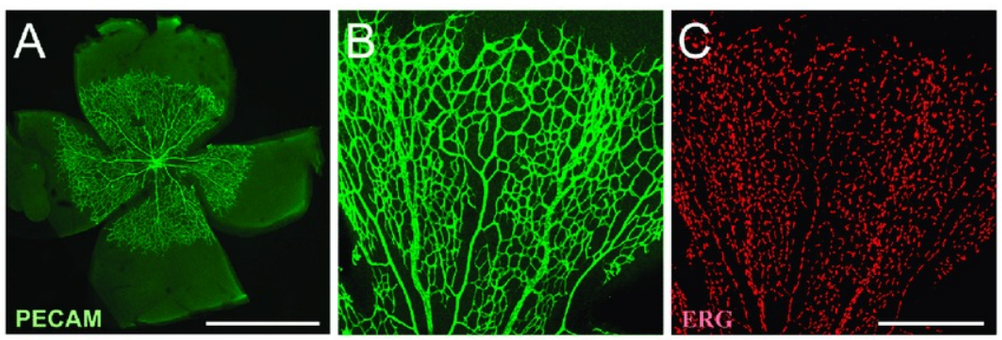
Metabolism

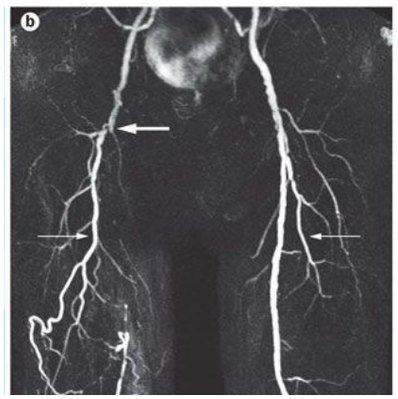
O_2 sensing

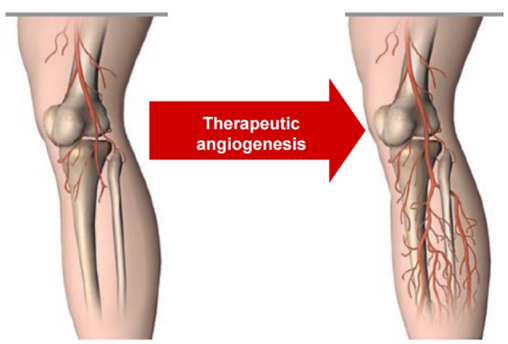
Redox



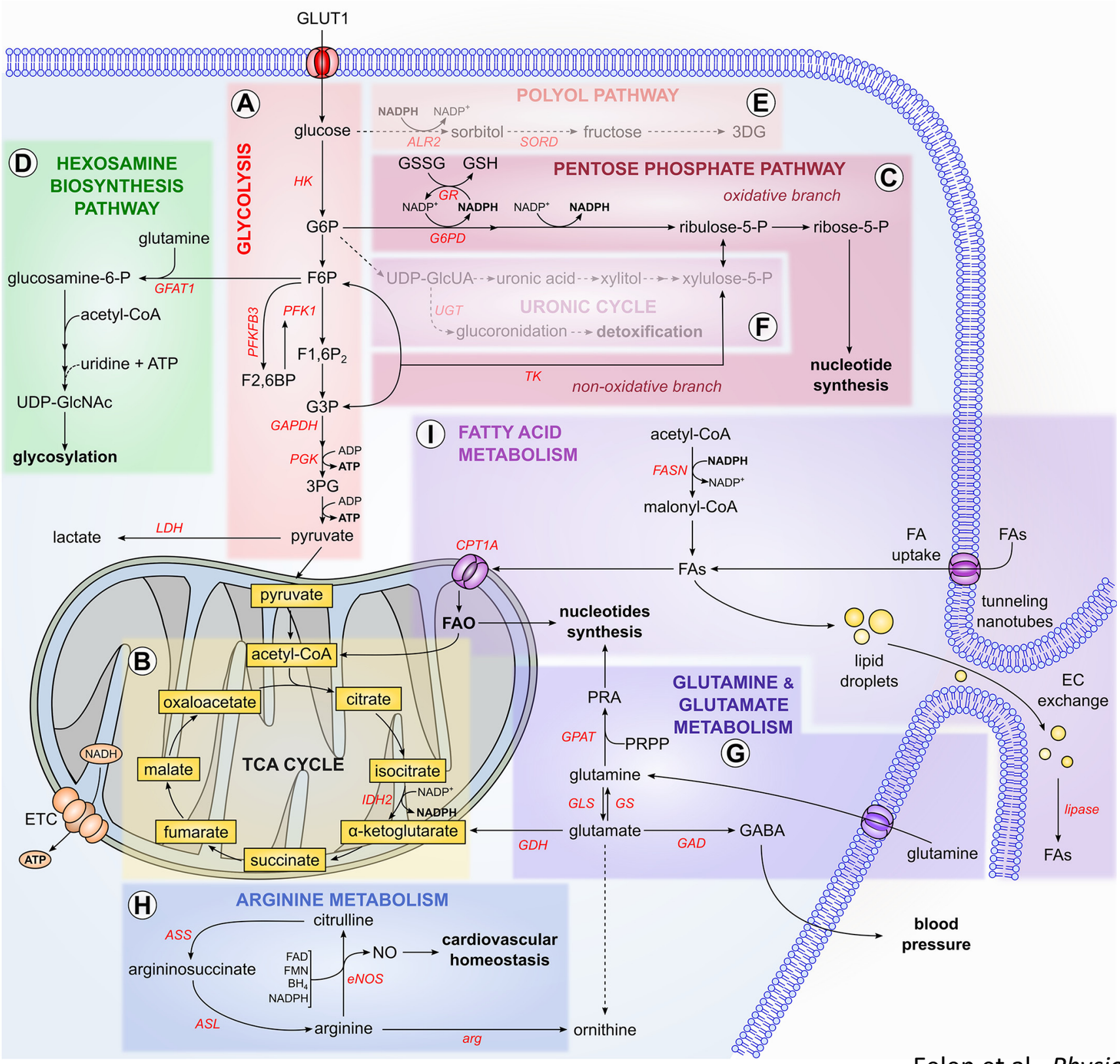








Endothelial metabolic pathways

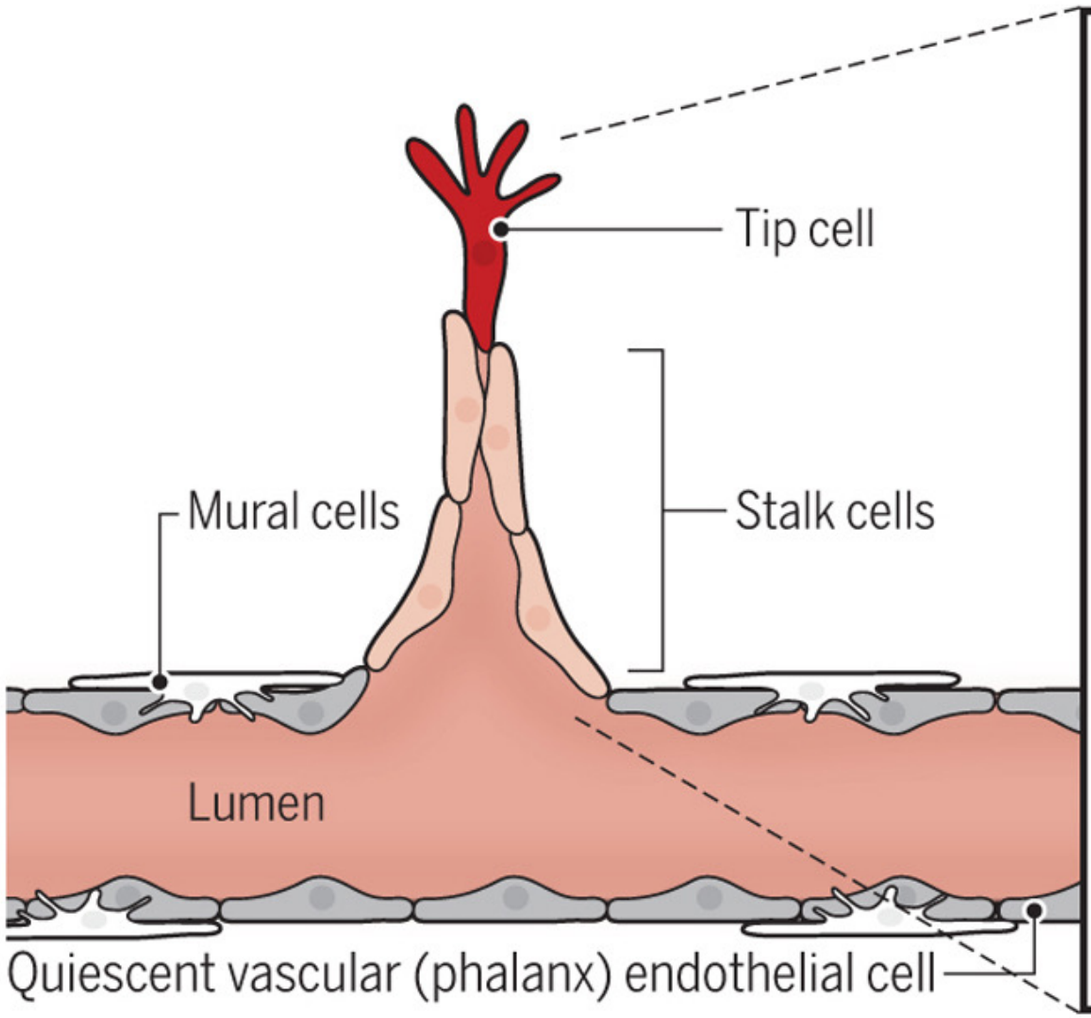


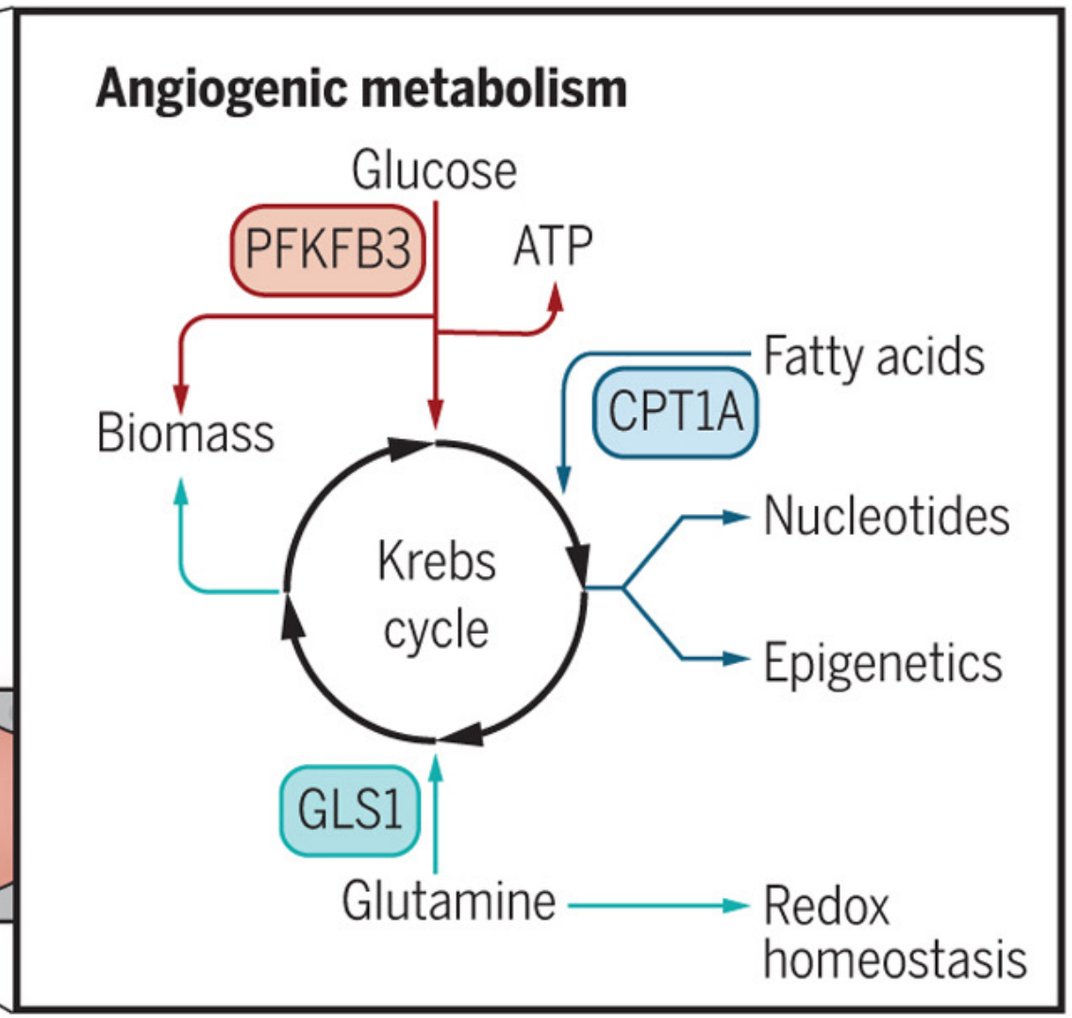
Eelen et al., *Physiological review*, 2017

Decoding endothelial metabolism

Metabolic pathways in angiogenesis

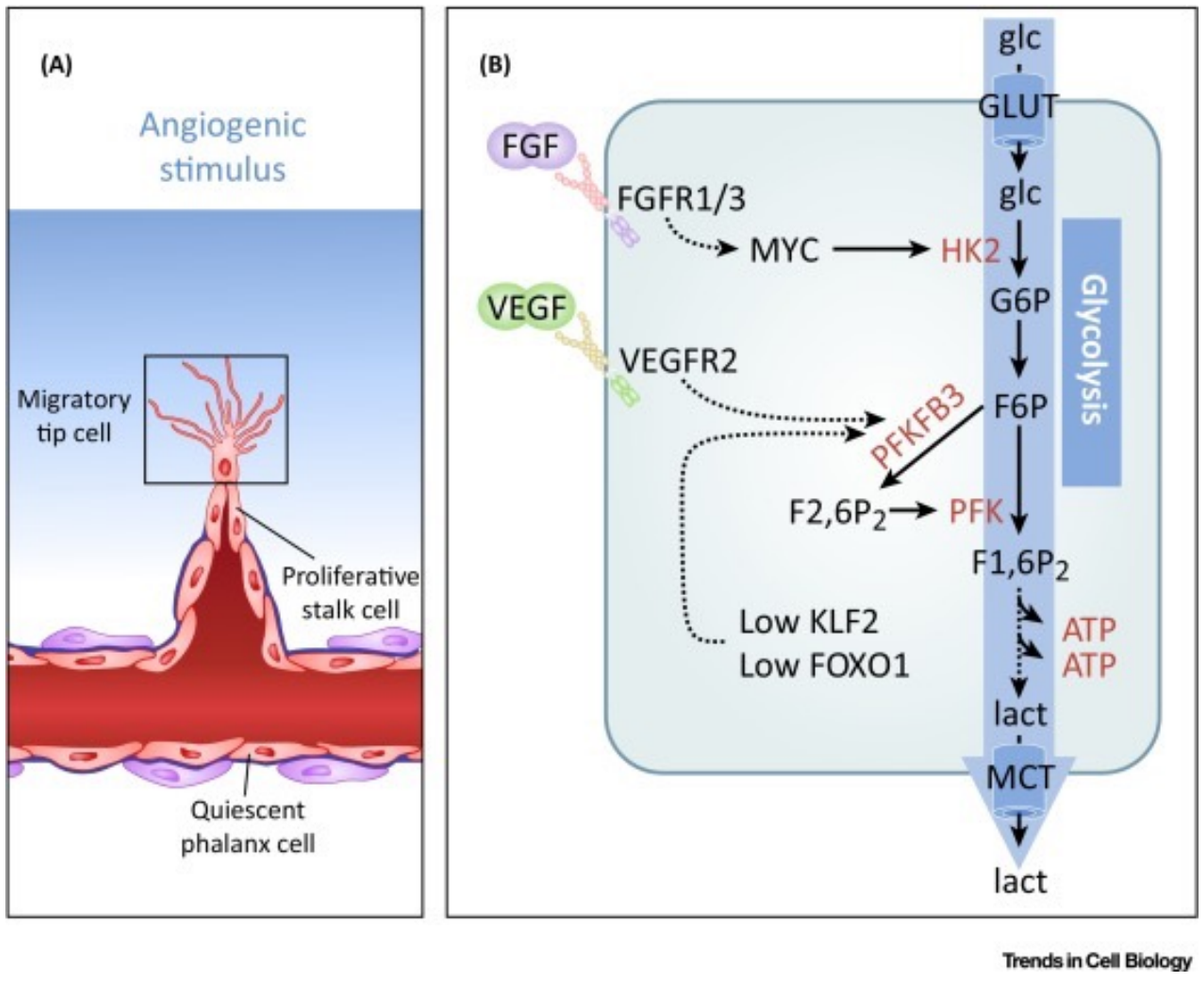
During angiogenesis, endothelial cells undergo metabolic changes that facilitate the formation of a sprout by stalk cells, which is directed by the tip cell. Key regulators of endothelial cell metabolism, PFKFB3, CPT1A, and GLS1, might be new therapeutic targets for various conditions.





Li and Carmeliet, 2018

Endothelial growth factors and their receptors control metabolism and metabolic pathways



Rohelenova et al., 2018

LETTER

doi:10.1038/nature22322

FGF–dependent metabolic control of vascular development

Pengchun Yu[1], Kerstin Wilhelm[2]*, Alexandre Dubrac[1]*, Joe K. Tung[1]*, Tiago C. Alves[3], Jennifer S. Fang[1], Yi Xie[1], Jie Zhu[4], Zehua Chen[5], Frederik De Smet[6,7], Jiasheng Zhang[1], Suk-Won Jin[1,8], Lele Sun[9], Hongye Sun[9], Richard G. Kibbey[3], Karen K. Hirschi[1], Nissim Hay[10], Peter Carmeliet[11,12], Thomas W. Chittenden[5], Anne Eichmann[1,13], Michael Potente[2] & Michael Simons[1,14]

LETTERS

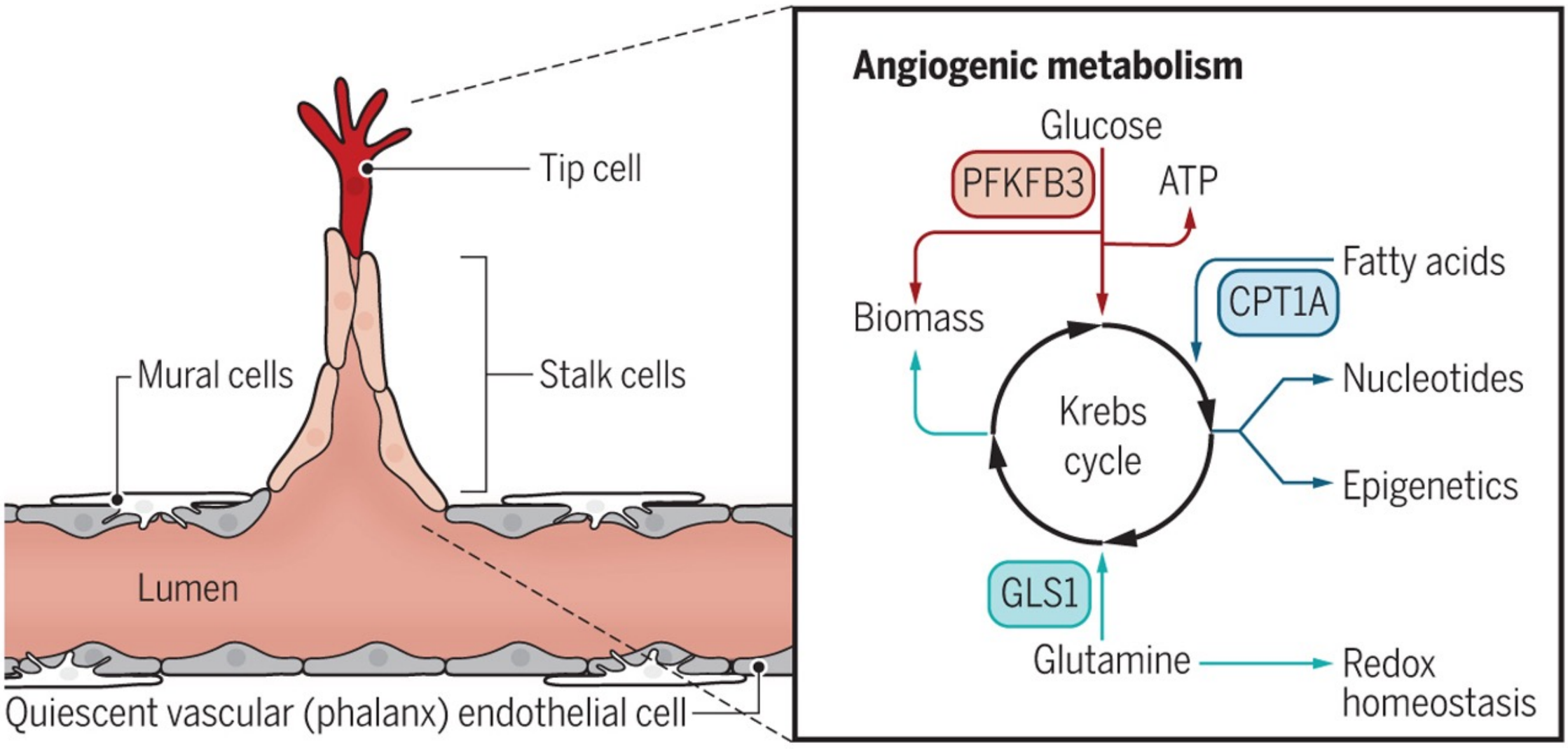
Vascular endothelial growth factor B controls endothelial fatty acid uptake

Carolina E. Hagberg[1,2], Annelie Falkevall[1,2], Xun Wang[1,2], Erik Larsson[3], Jenni Huusko[4], Ingrid Nilsson[1], Laurens A. van Meeteren[5], Erik Samen[6,7], Li Lu[7], Maarten Vanwildemeersch[1,2], Joakim Klar[2,5], Guillem Genove[8], Kristian Pietras[1,2], Sharon Stone-Elander[6,7], Lena Claesson-Welsh[5], Seppo Ylä-Herttuala[4], Per Lindahl[3,9] & Ulf Eriksson[1,2]

Open question:

Do metabolites and metabolic pathways regulate endothelial growth factor receptors ?

Key metabolic pathways in endothelial cells



Li and Carmeliet, 2018

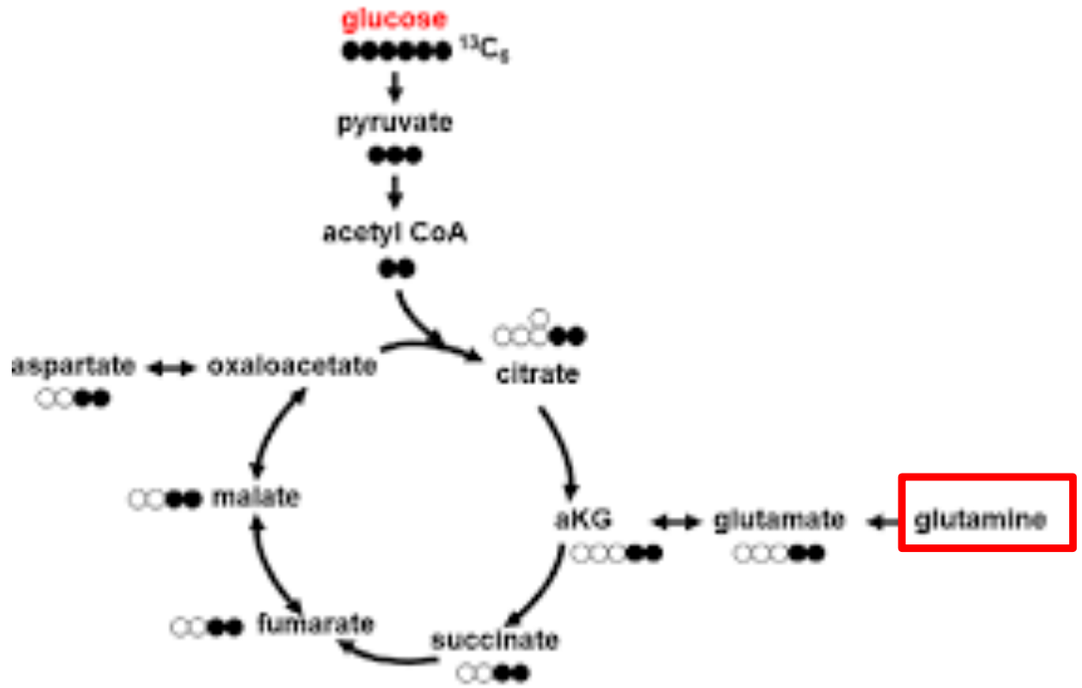
Arterial concentrations of free amino acids in whole blood and plasma

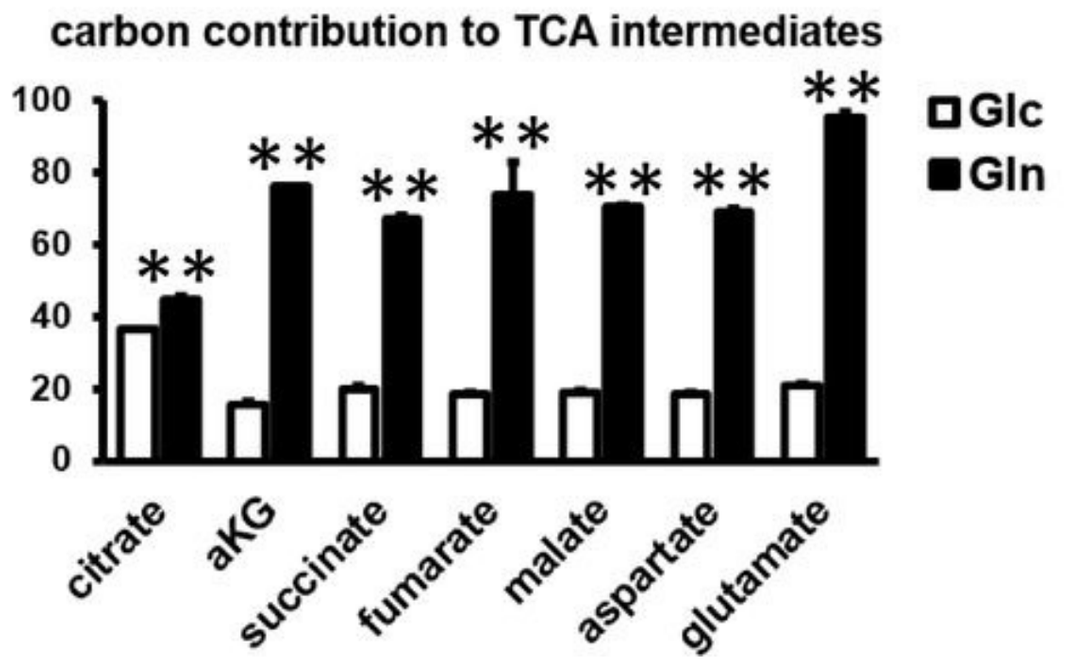
	Whole blood (μM)	Plasma (μM)	P*
Taurine	207.0 ± 26.4	39.4 ± 3.1	<0.001
Aspartate	186.3 ± 16.0	—	—
Threonine	138.7 ± 11.6	112.4 ± 9.1	<0.01
Serine	166.9 ± 10.3	121.1 ± 7.9	<0.001
Glutamine†	587.7 ± 34.3	565.0 ± 21.1	NS
Proline	192.1 ± 16.5	167.3 ± 8.4	NS
Citrulline	50.7 ± 3.5	35.9 ± 3.0	<0.005
Glycine	337.4 ± 20.2	201.0 ± 15.1	<0.001
Alanine	291.7 ± 21.8	225.4 ± 17.8	<0.005
α-Amino-butyrate	25.9 ± 4.1	26.8 ± 4.1	NS
Valine	251.6 ± 20.2	236.1 ± 15.1	NS
Cystine	—	111.3 ± 11.5	—
Methionine	15.9 ± 1.6	18.9 ± 1.9	NS
Isoleucine	62.4 ± 5.1	58.9 ± 3.0	NS
Leucine	130.1 ± 10.3	126.4 ± 6.0	NS
Tyrosine	61.1 ± 4.6	53.9 ± 3.6	NS
Phenylalanine	54.3 ± 3.8	53.4 ± 2.7	NS

* P = significance of difference between whole blood and plasma concentration (paired t-test).

Felig *et al.*, PNAS 1973

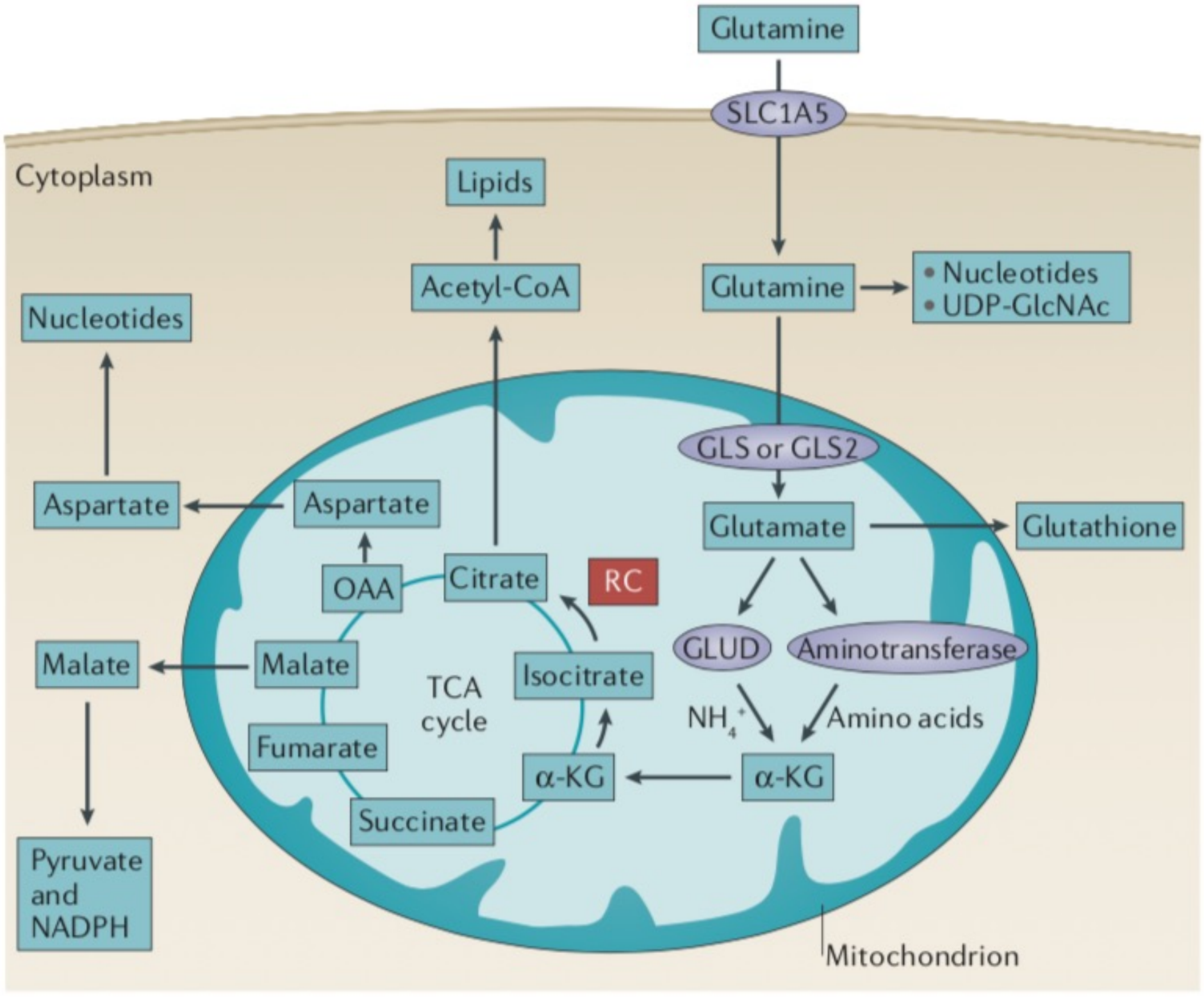
Comparison of glucose and glutamine consumption and fate in ECs





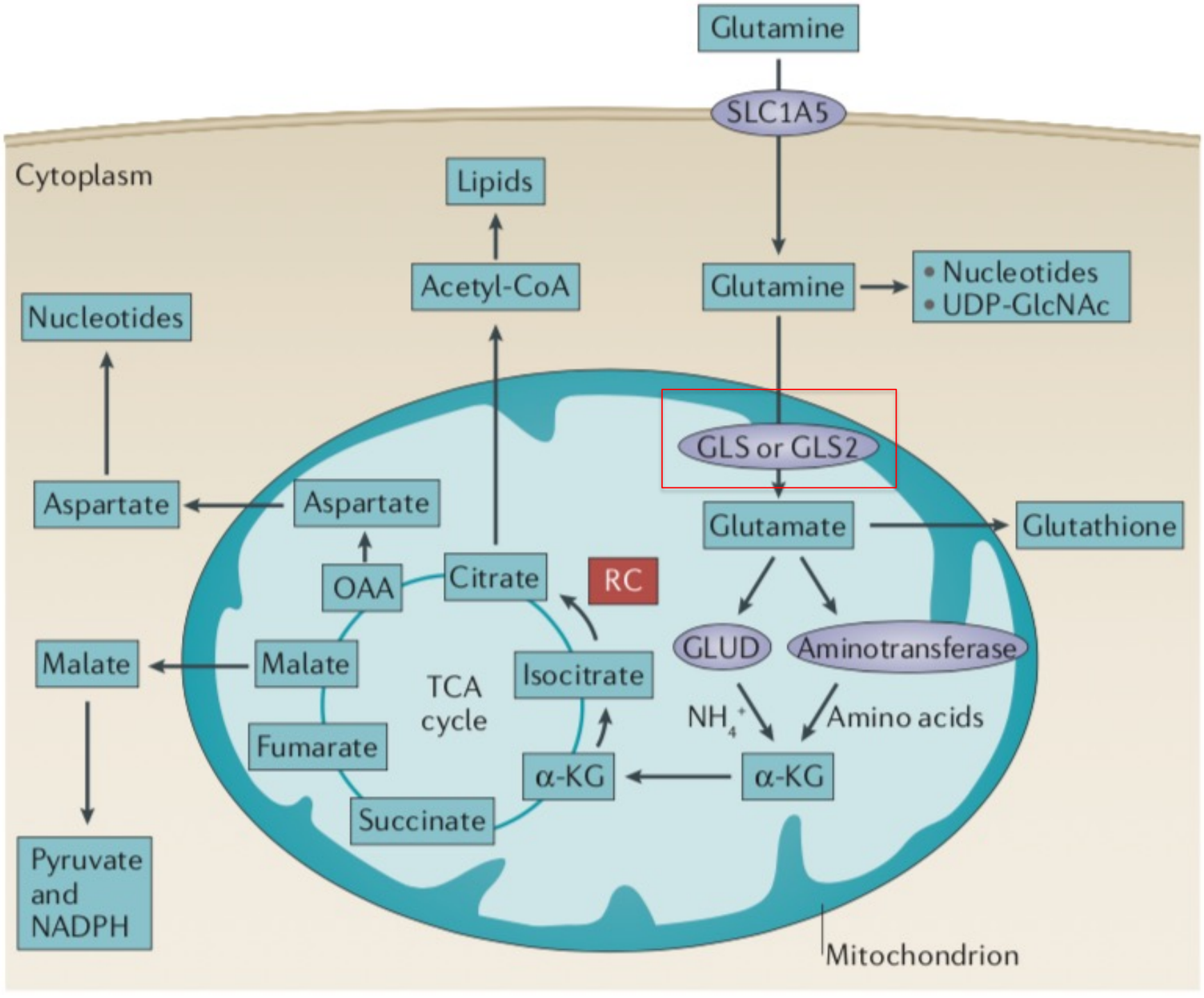
Kim et al., 2017

Glutamine metabolism



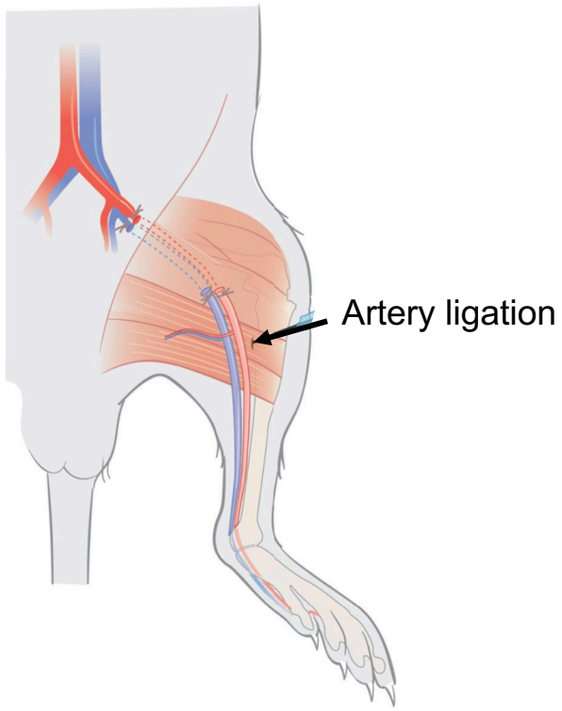
Altam et al., 2017

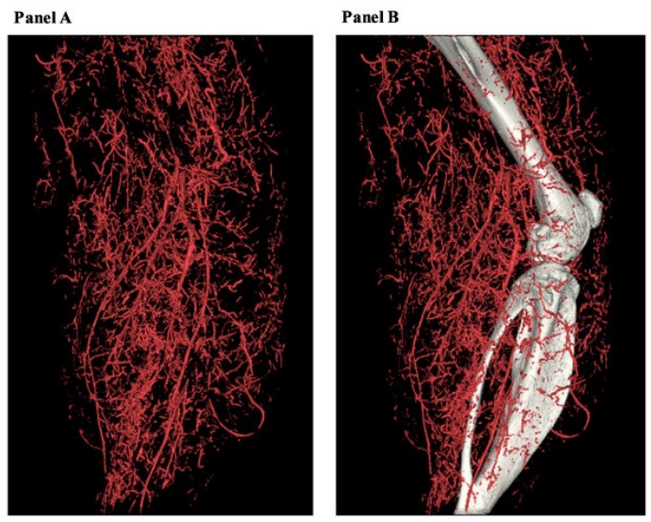
Genetic and pharmacological inhibition of glutamine metabolism (e.g. glutaminolysis)



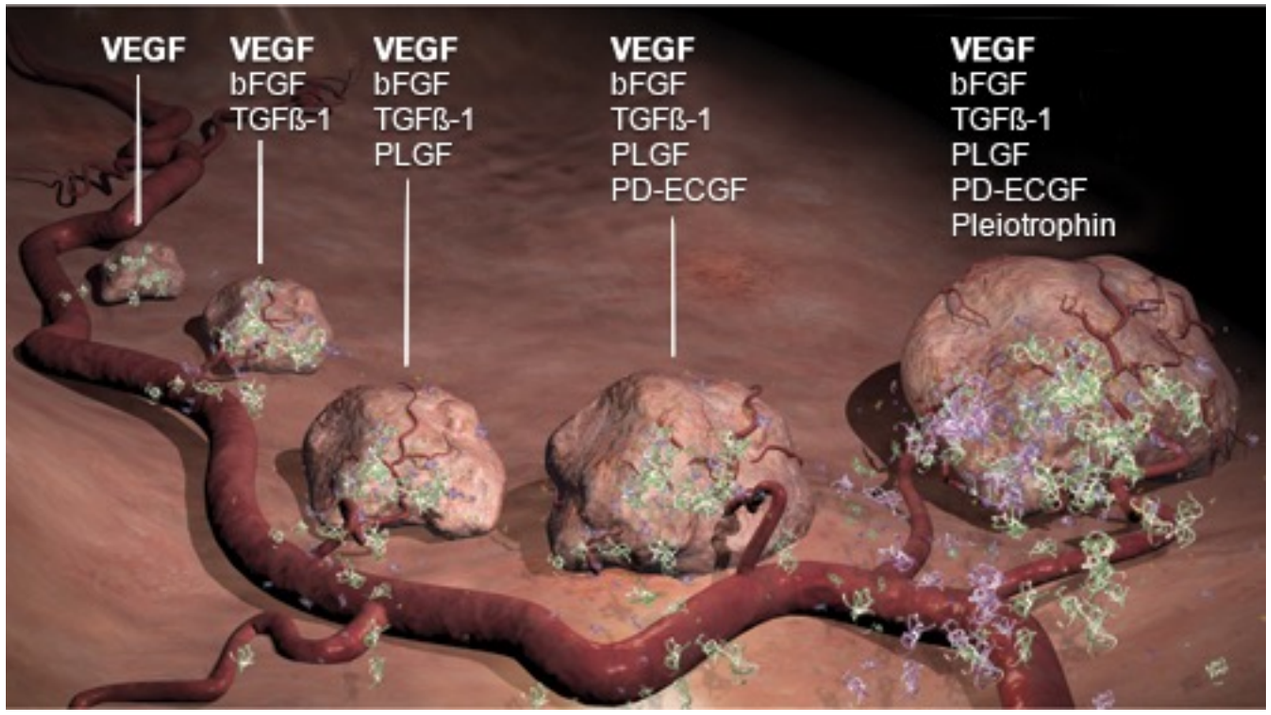
Altam et al., 2017

Is glutamine metabolism important during adult and pathological angiogenesis ?





Hindlimb ischaemia

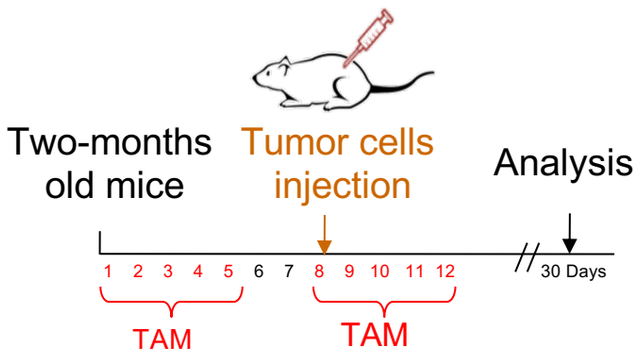


Tumor xenografts

Endothelial glutaminolysis is required during tumor growth

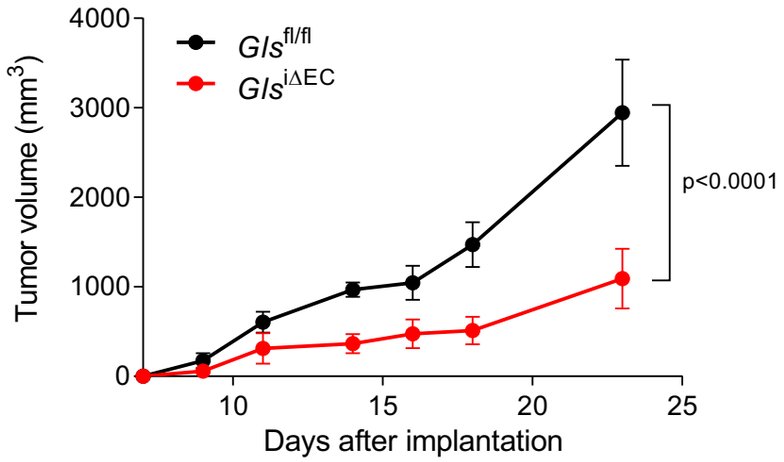
A

Tumor angiogenesis model

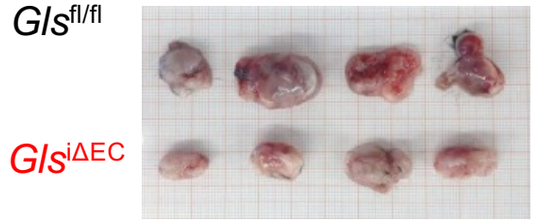


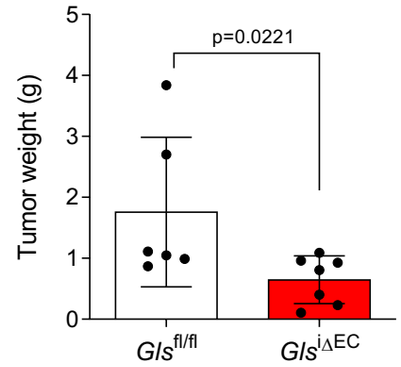
TAM=Tamoxifen

B

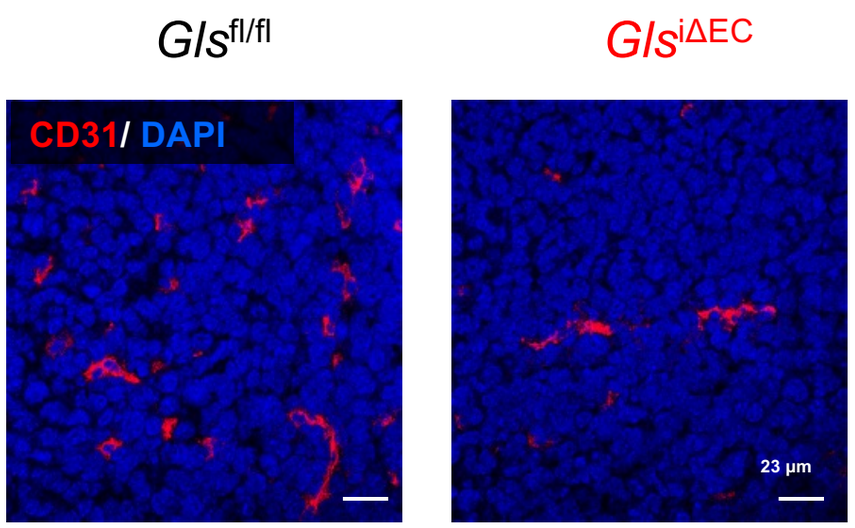


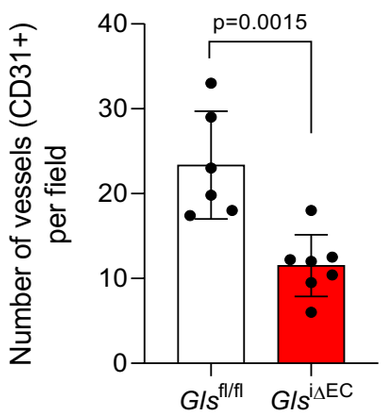
C





D





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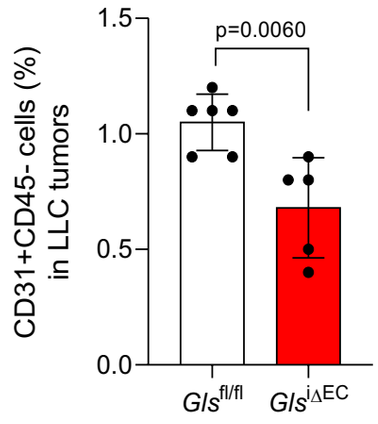
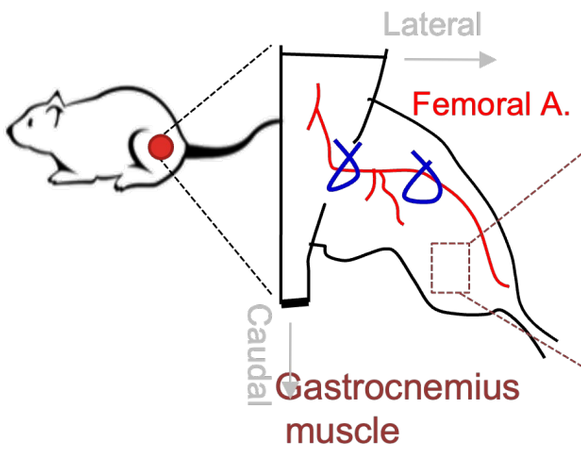
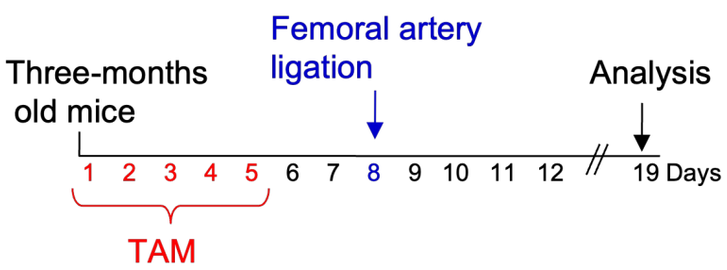


Endothelial glutaminolysis is required during ischemic angiogenesis

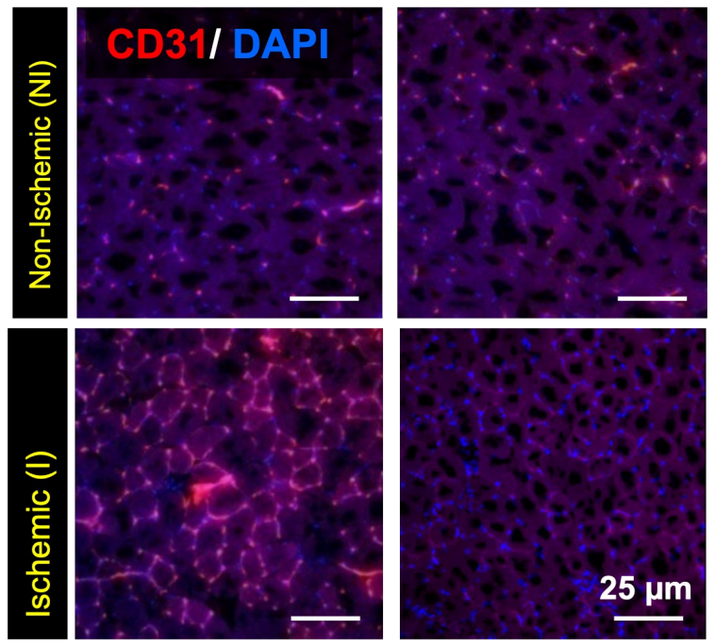
A

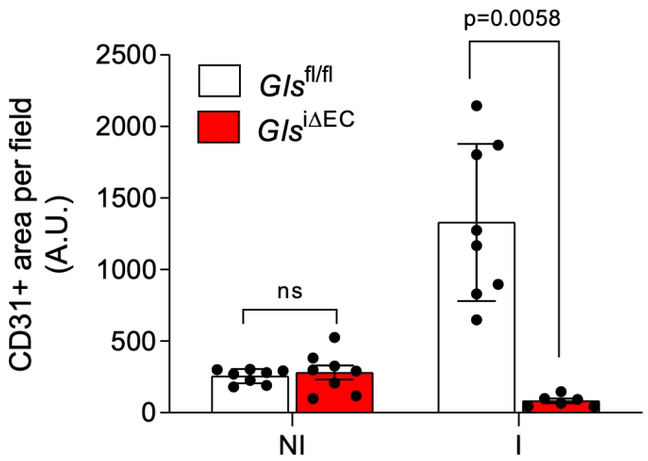
Hindlimb ischemia model



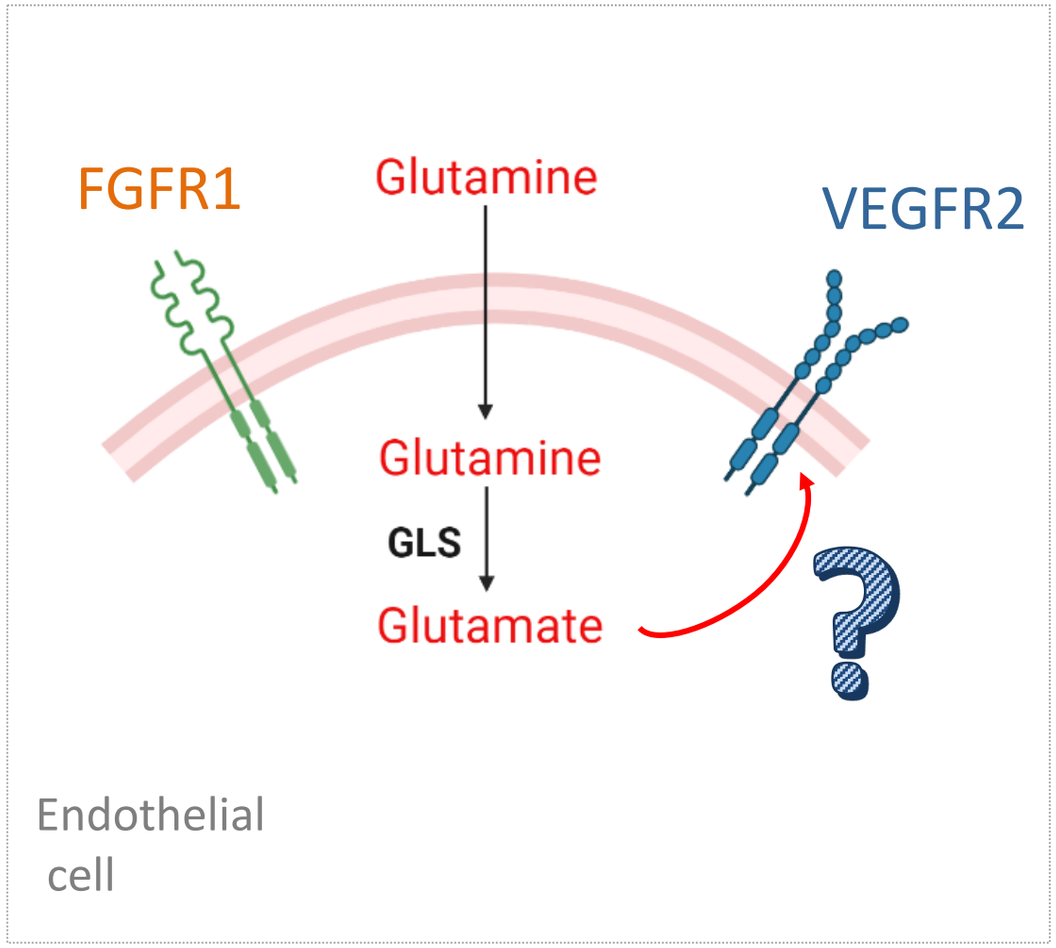


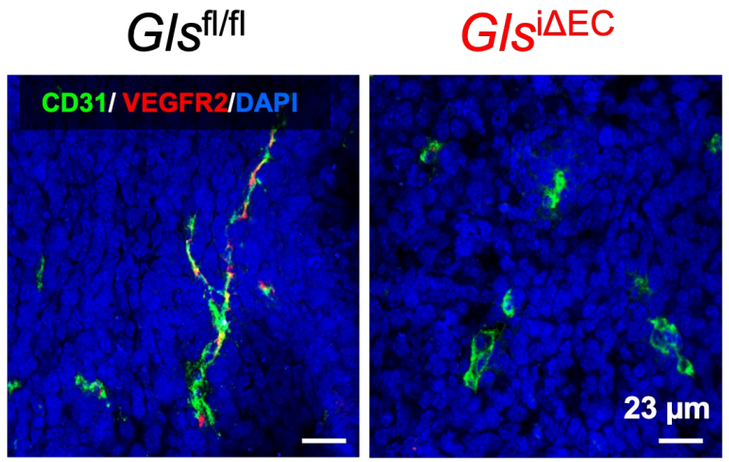
B

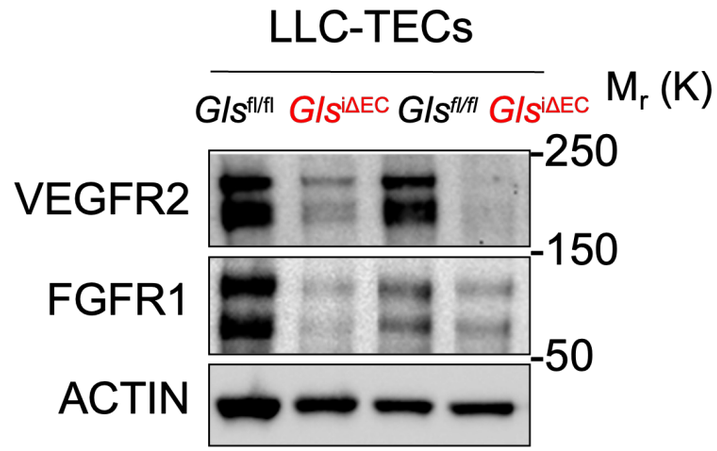


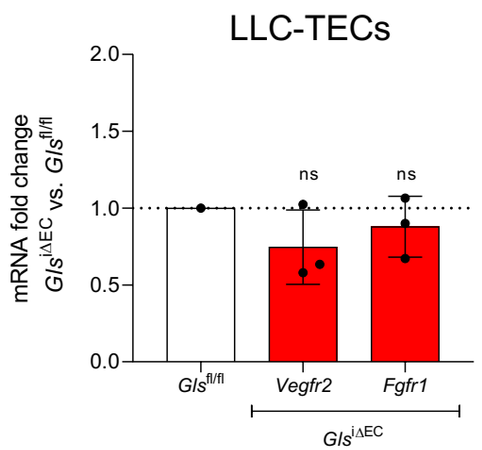


Endothelial glutaminolysis controls endothelial growth factor receptors synthesis

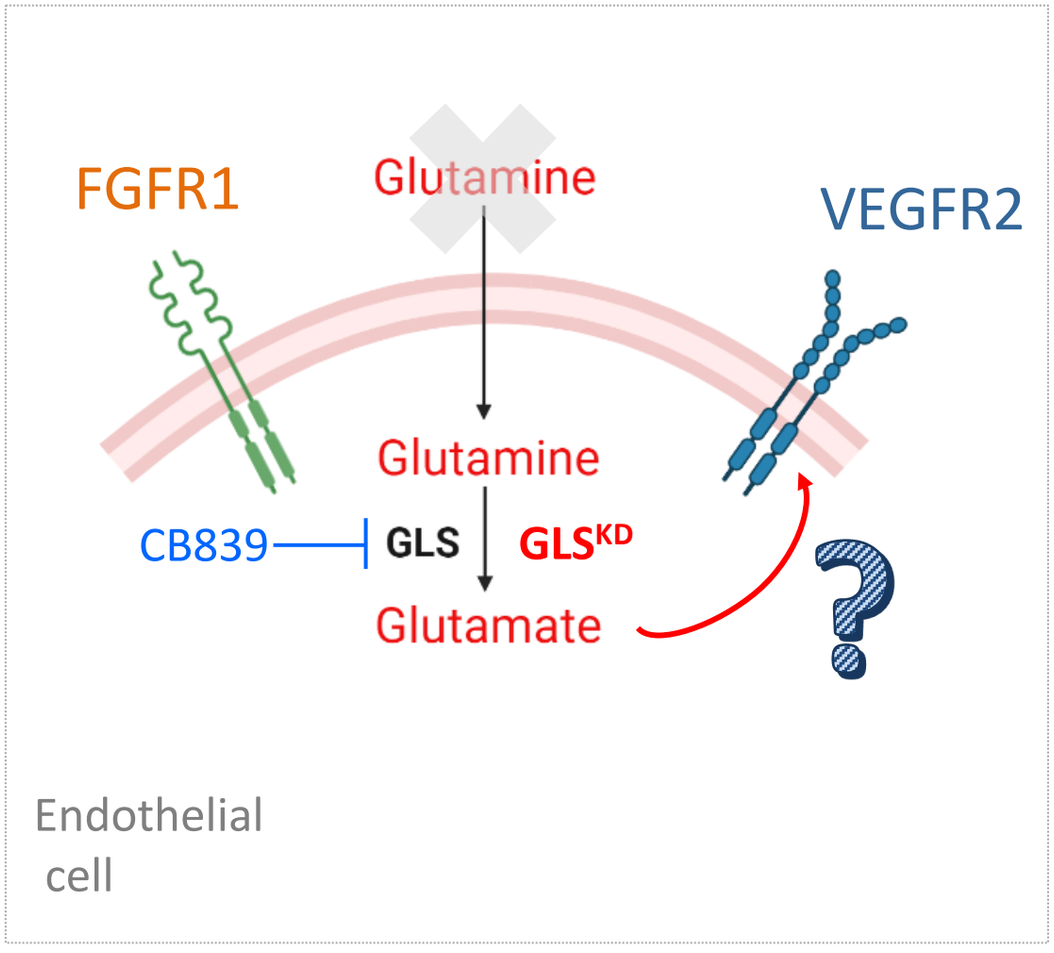


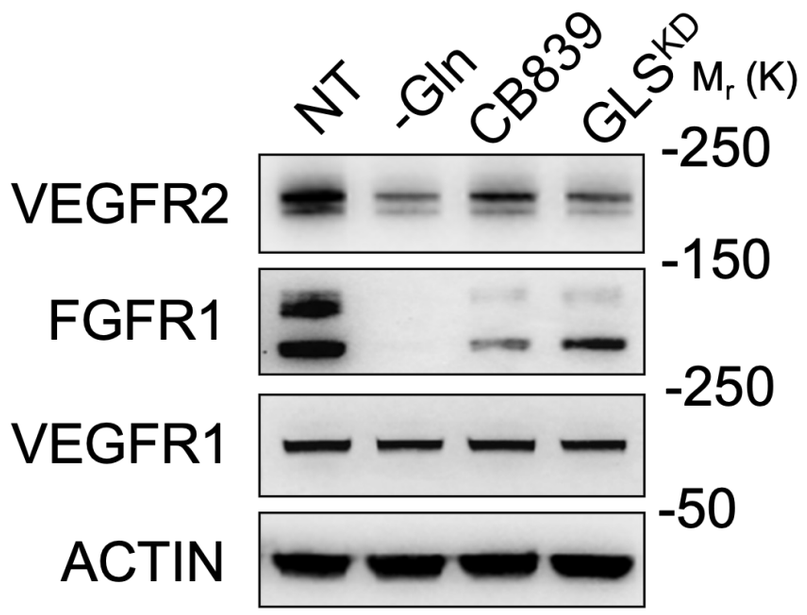


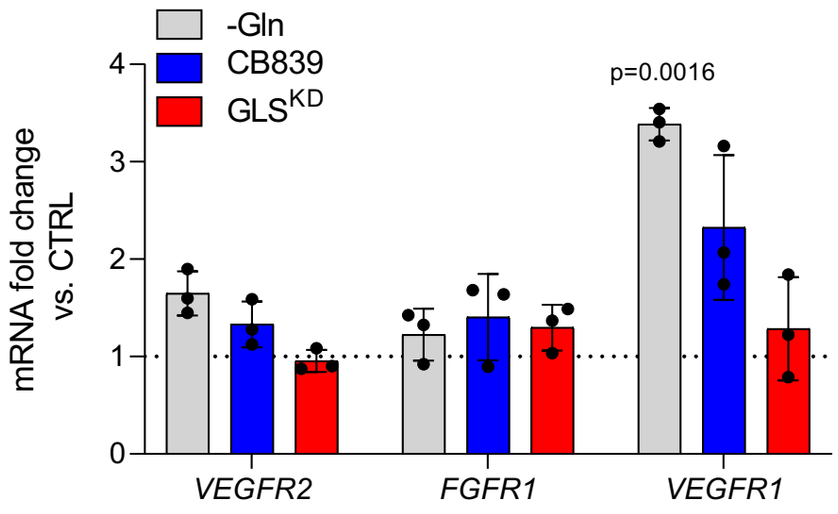




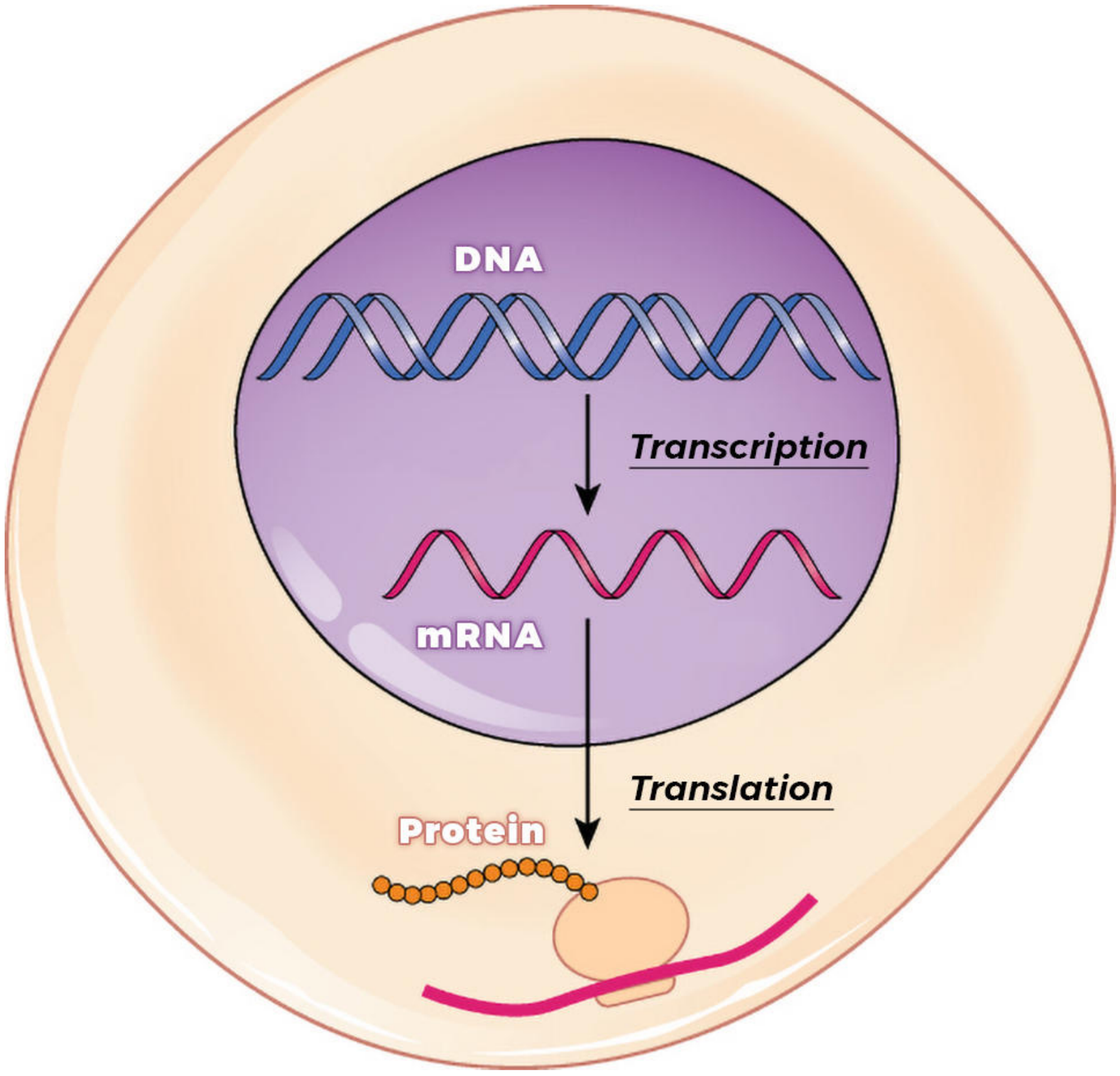
Endothelial glutaminolysis controls endothelial growth factor receptors synthesis



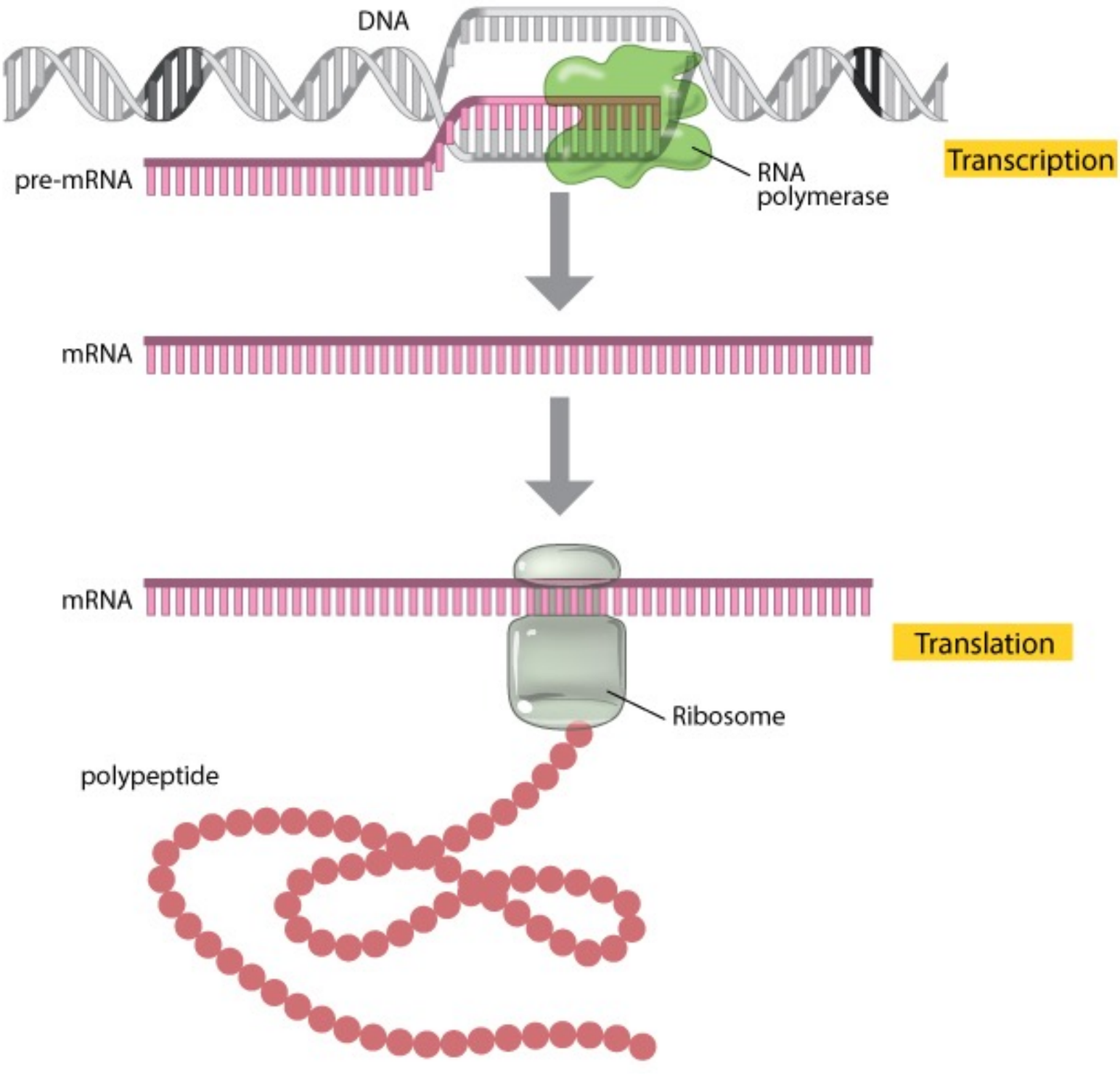




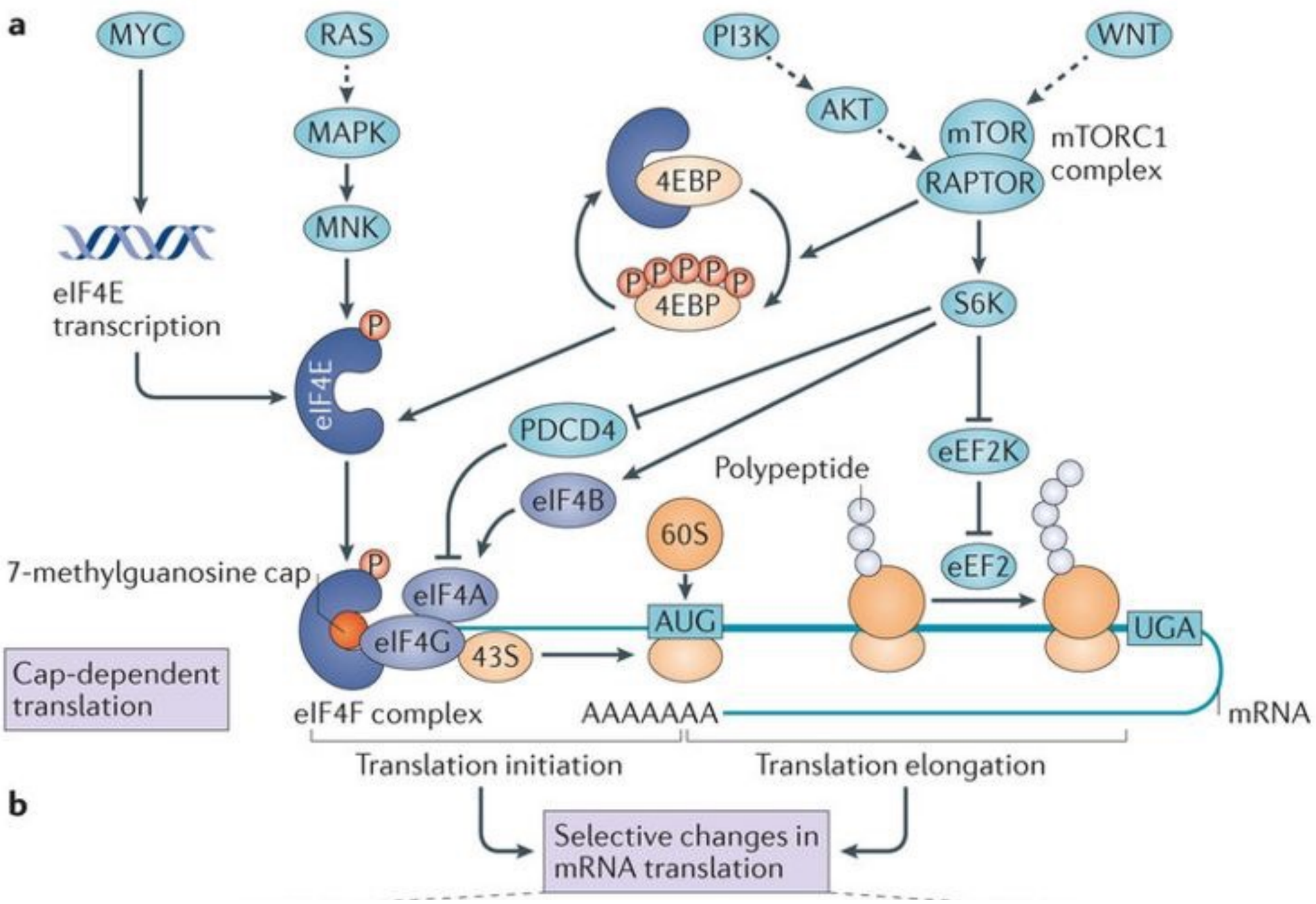
Transcription + Translation = Gene expression



Transcription and translation



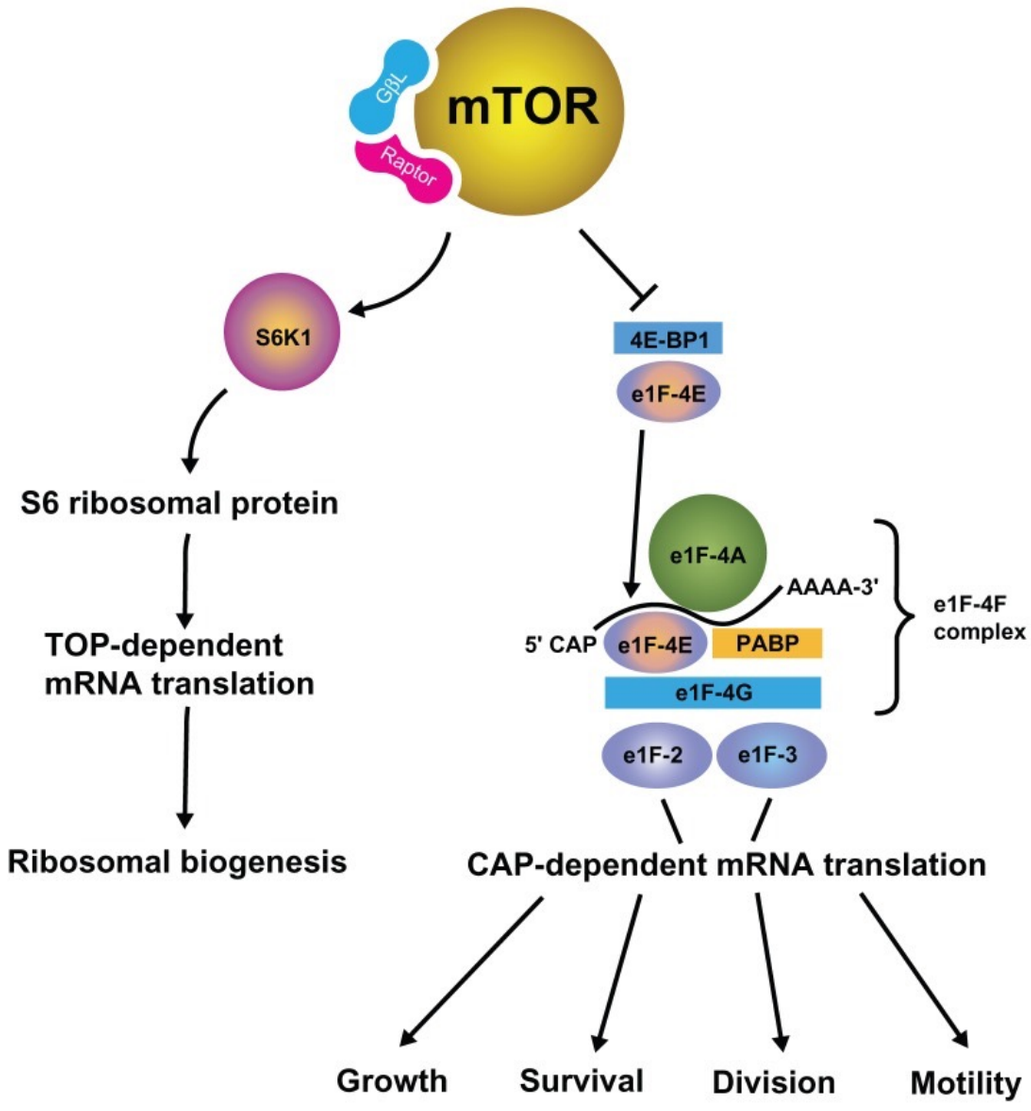
mRNA translation:
cooperation and integration of different signals



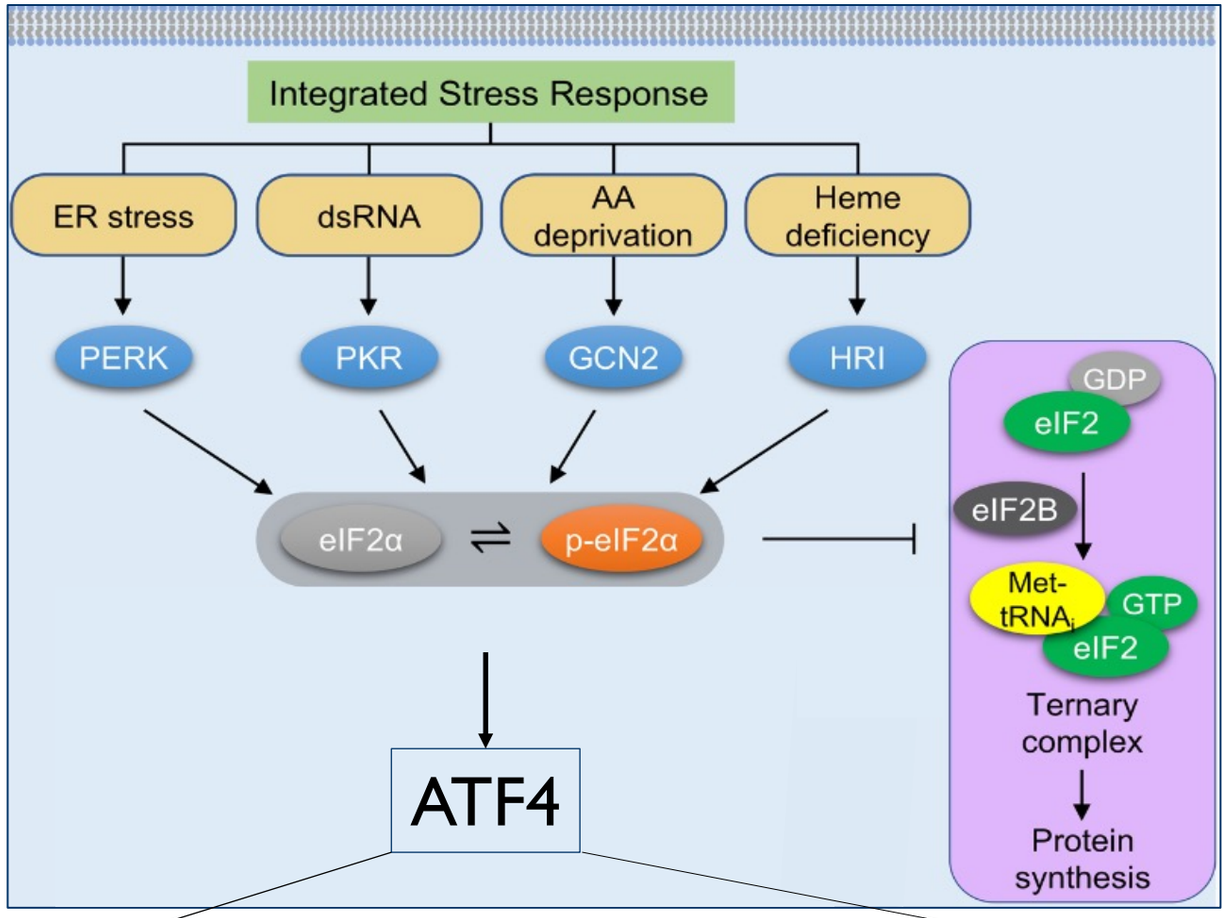
Truitt and Ruggero, 2016

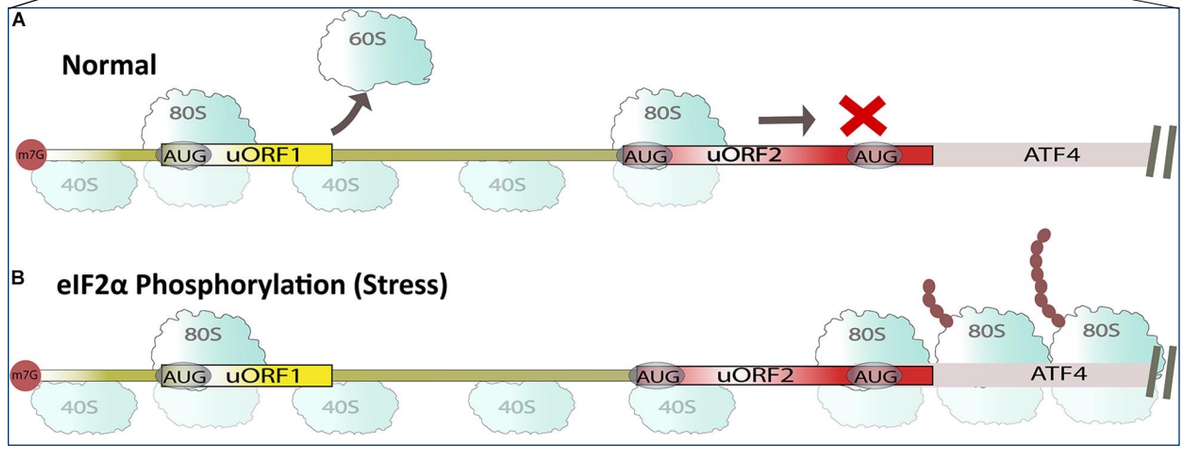
Signaling pathways regulating mRNA translation

mTORC1 pathway

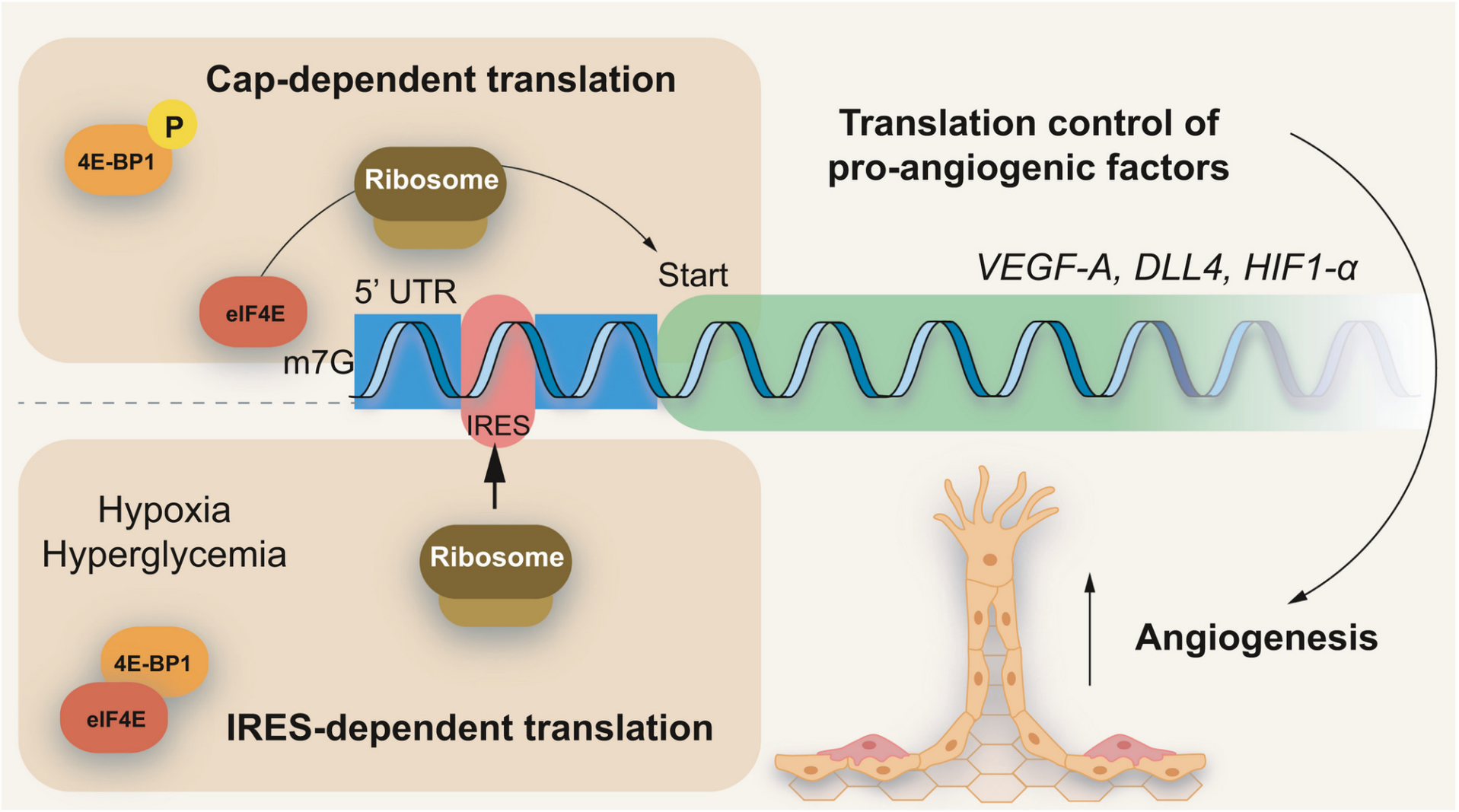


ISR pathway





Translation control of angiogenesis



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Internal Translation Initiation Mediated by the Angiogenic Factor Tie2*

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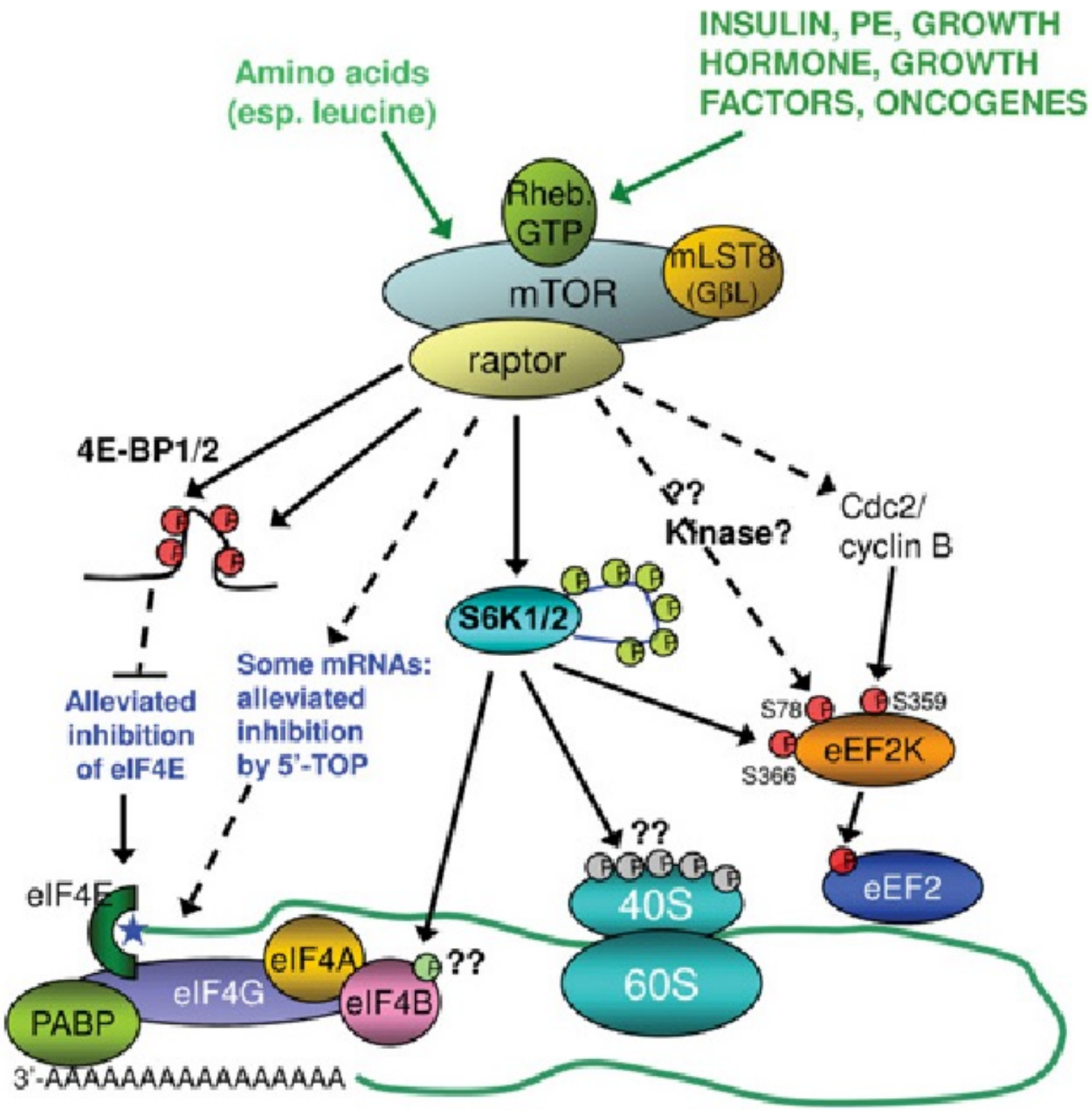
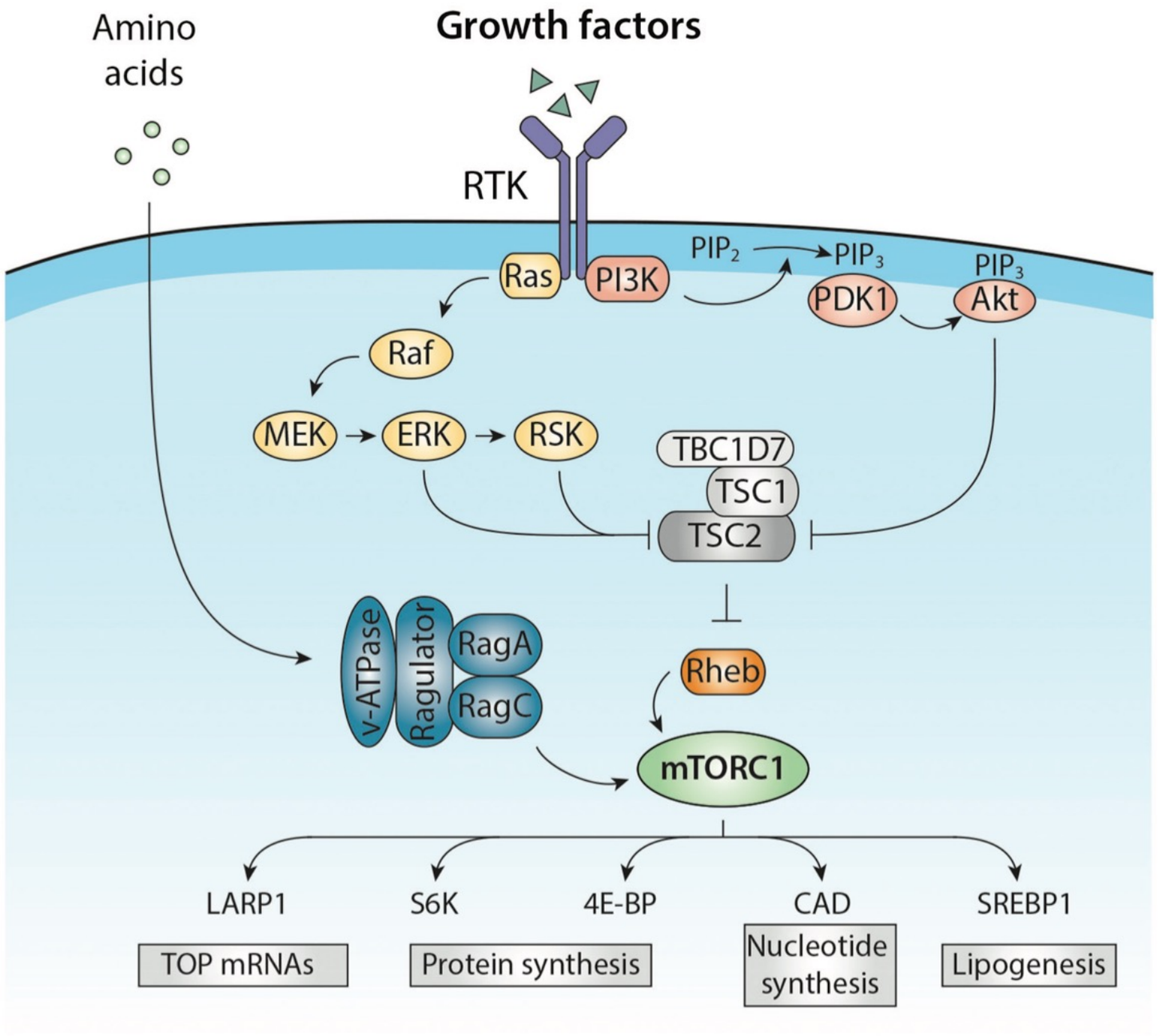
mTORC as a master control of mRNA translation

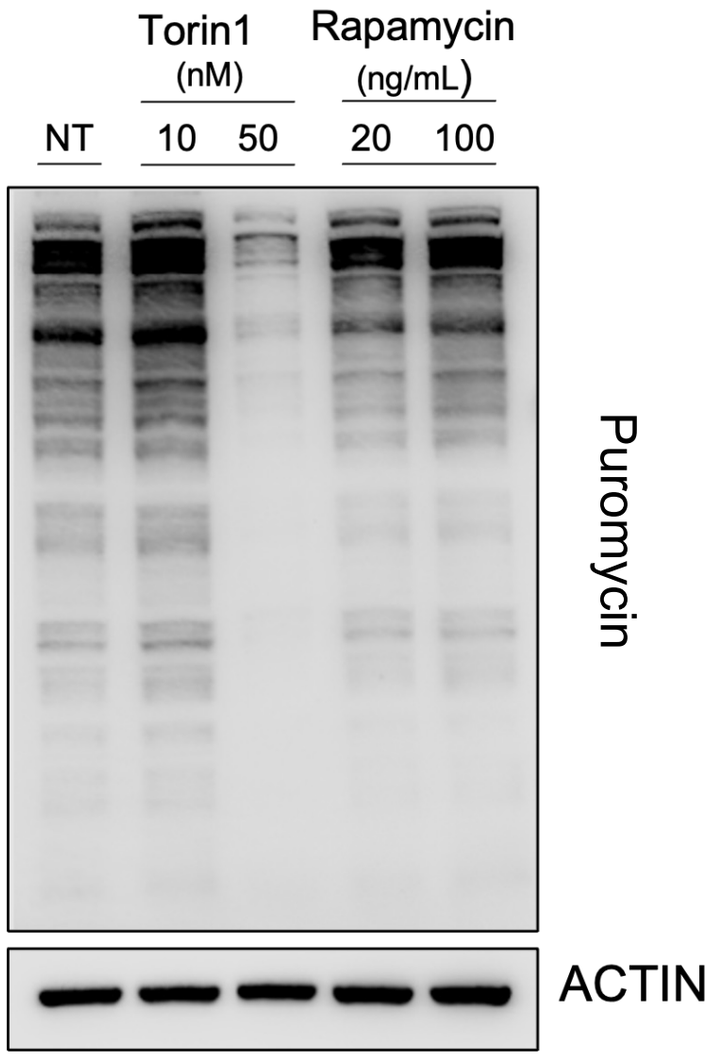


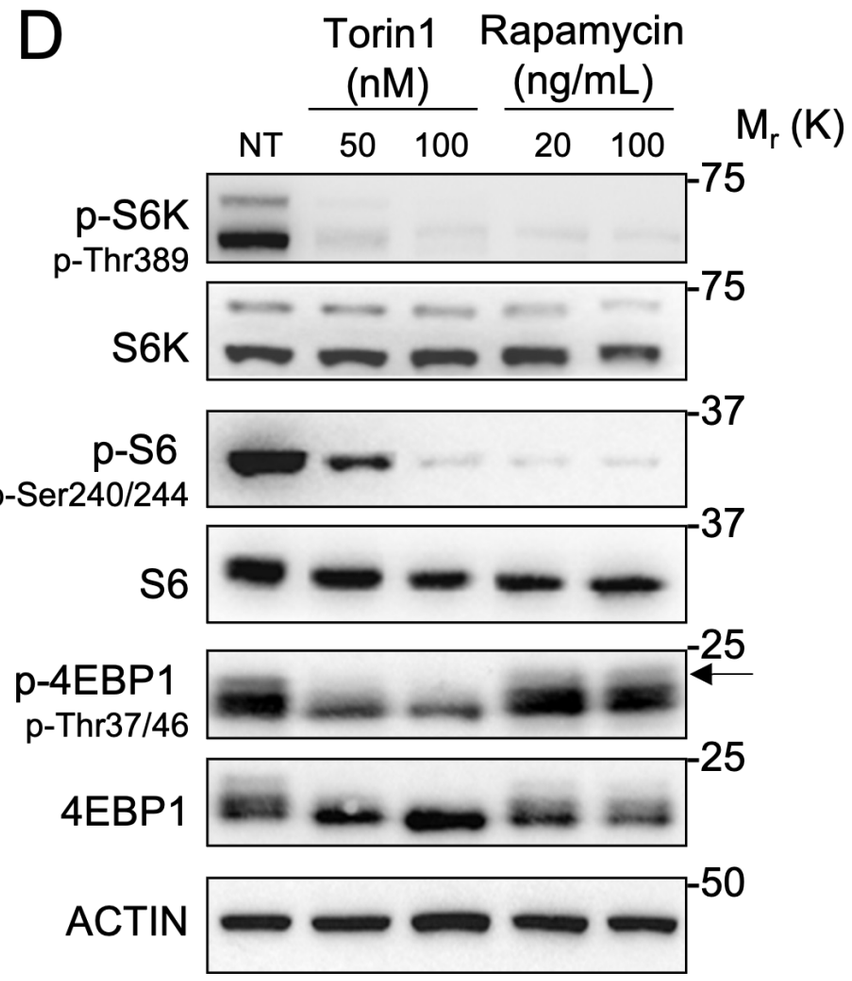
mTORC1 activation by amino acids and growth factors

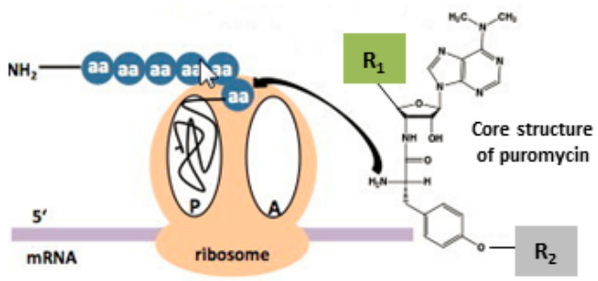


Cargnello et al., 2015

mTORC1-dependent controls of translation in ECs



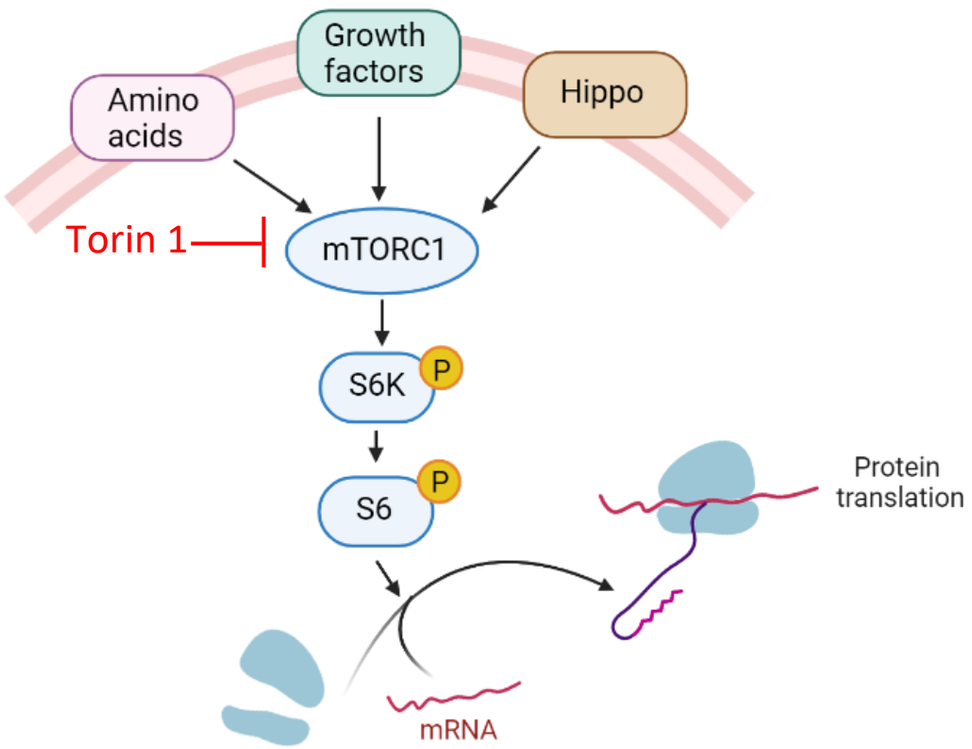


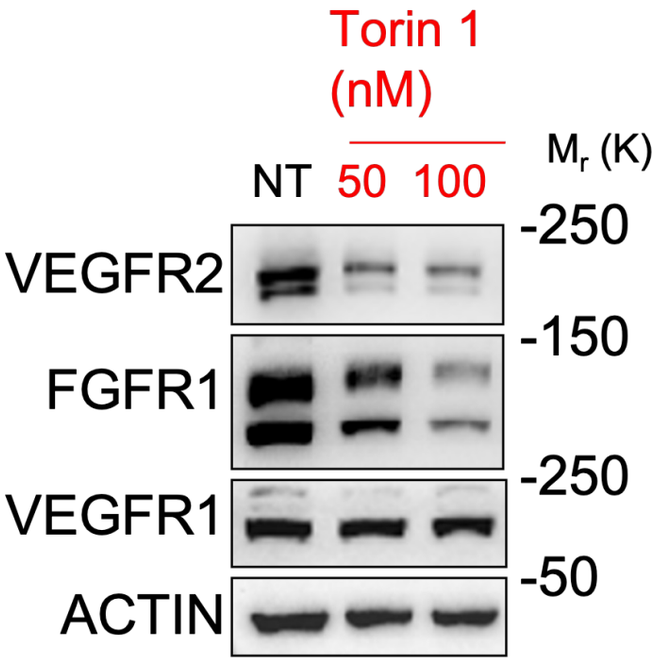


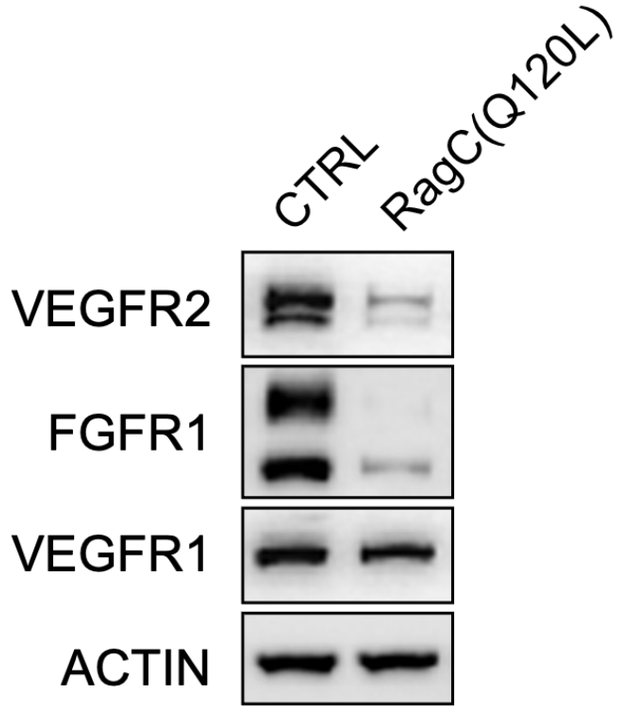
Puromycin labeling

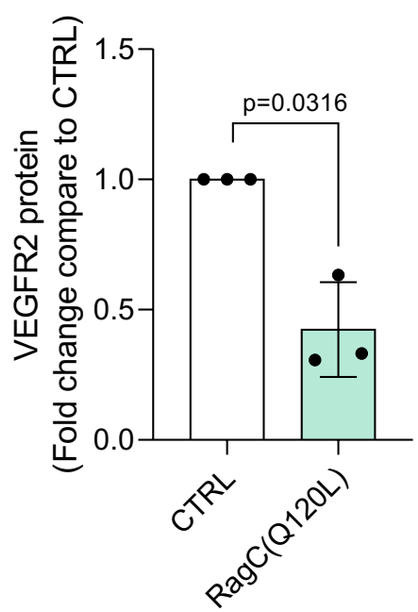
Surface sensing of translation (SUnSET)

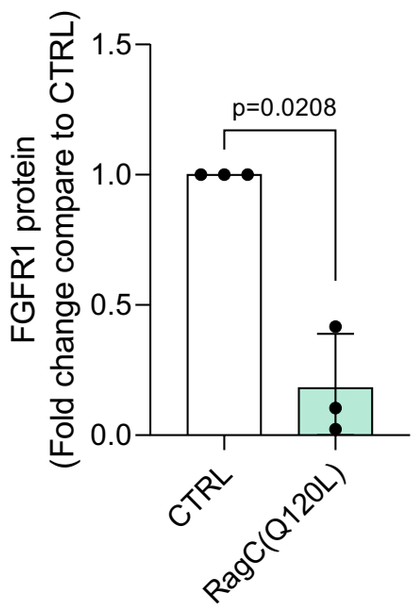
mTORC1 regulates endothelial growth factor receptors synthesis via glutaminolysis

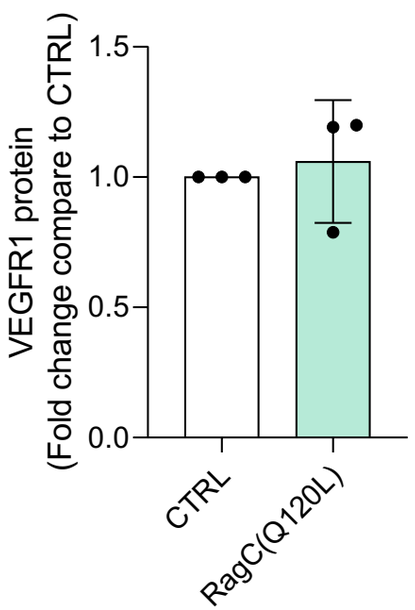




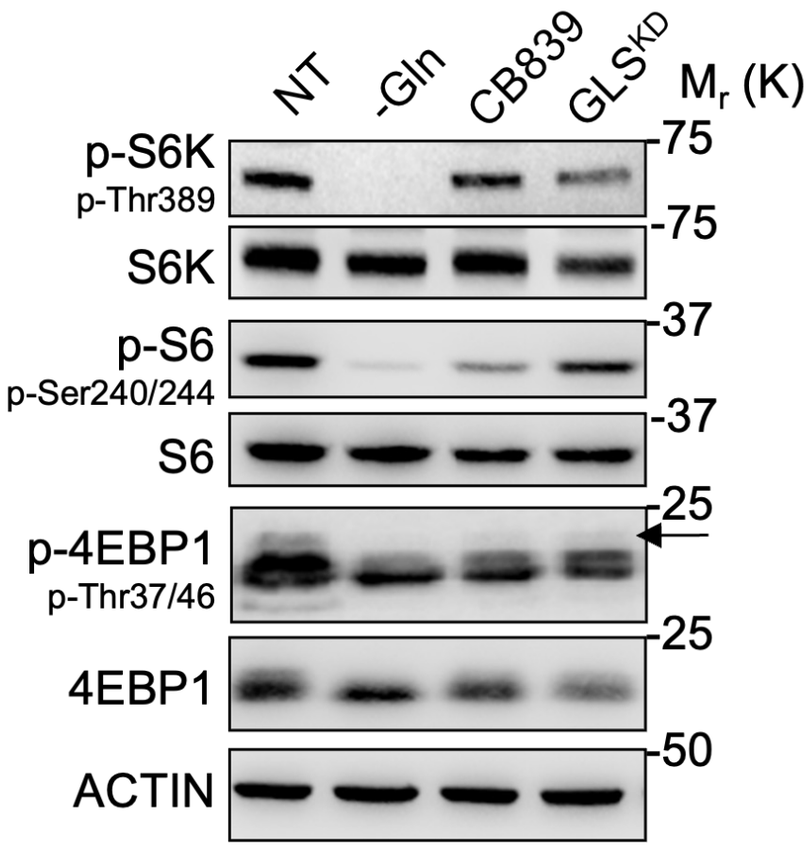


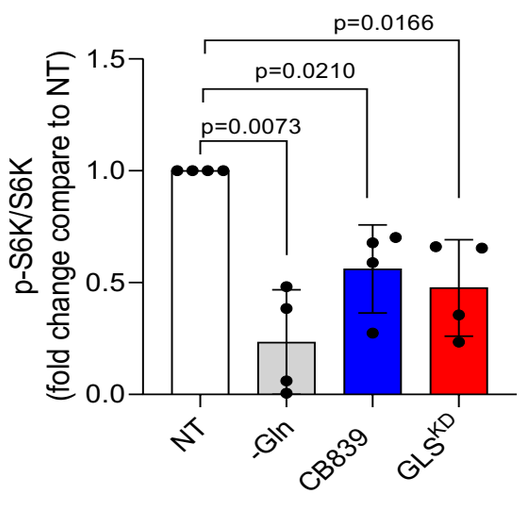


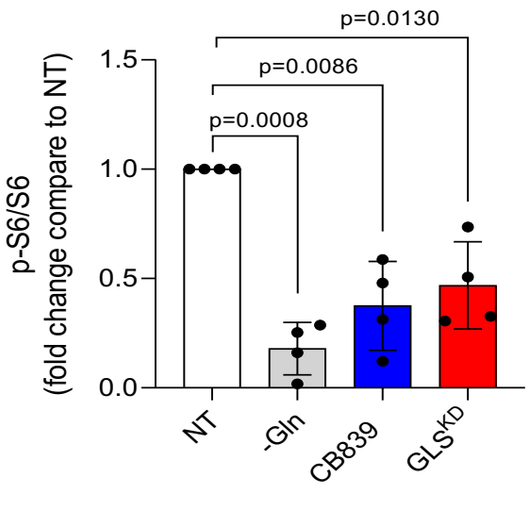


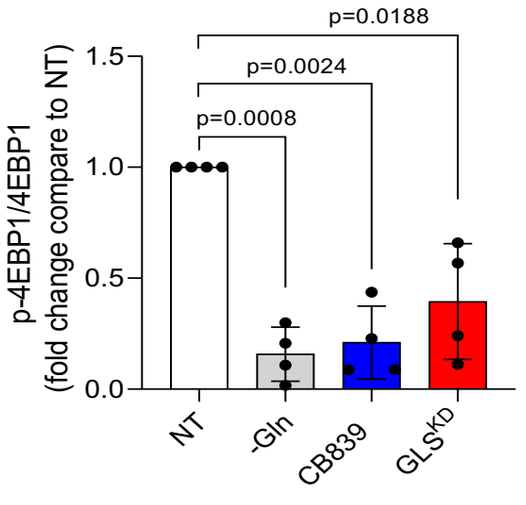


Glutaminolysis regulates endothelial growth factor receptors synthesis via mTORC

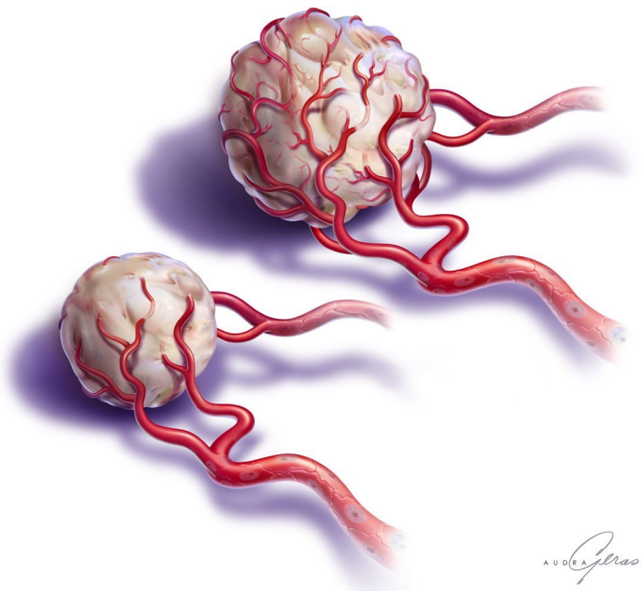








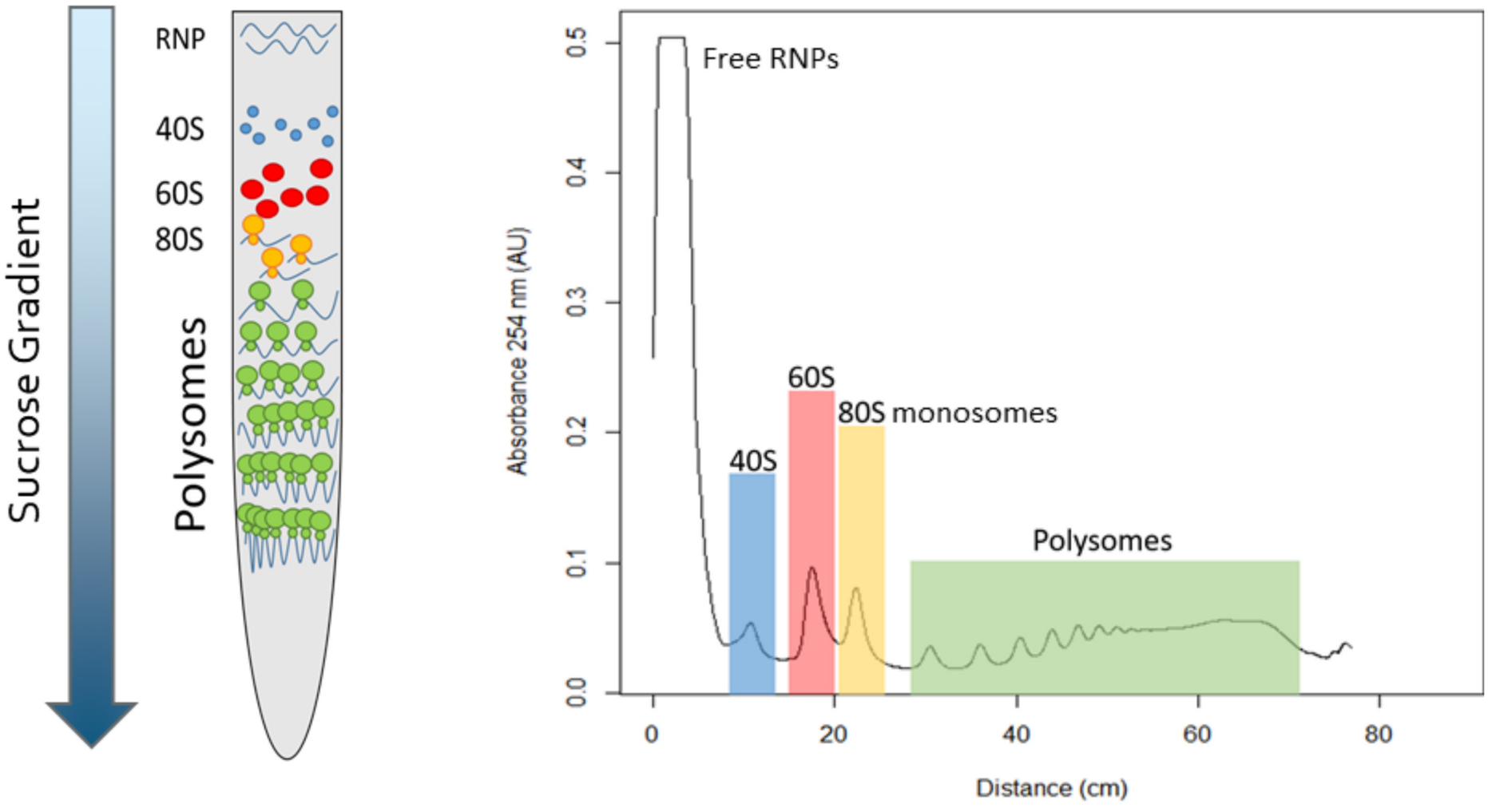
Endothelial-specific deletion of *GLS1* affects mTORC1 activation and VEGFR2 translation in tumor ECs



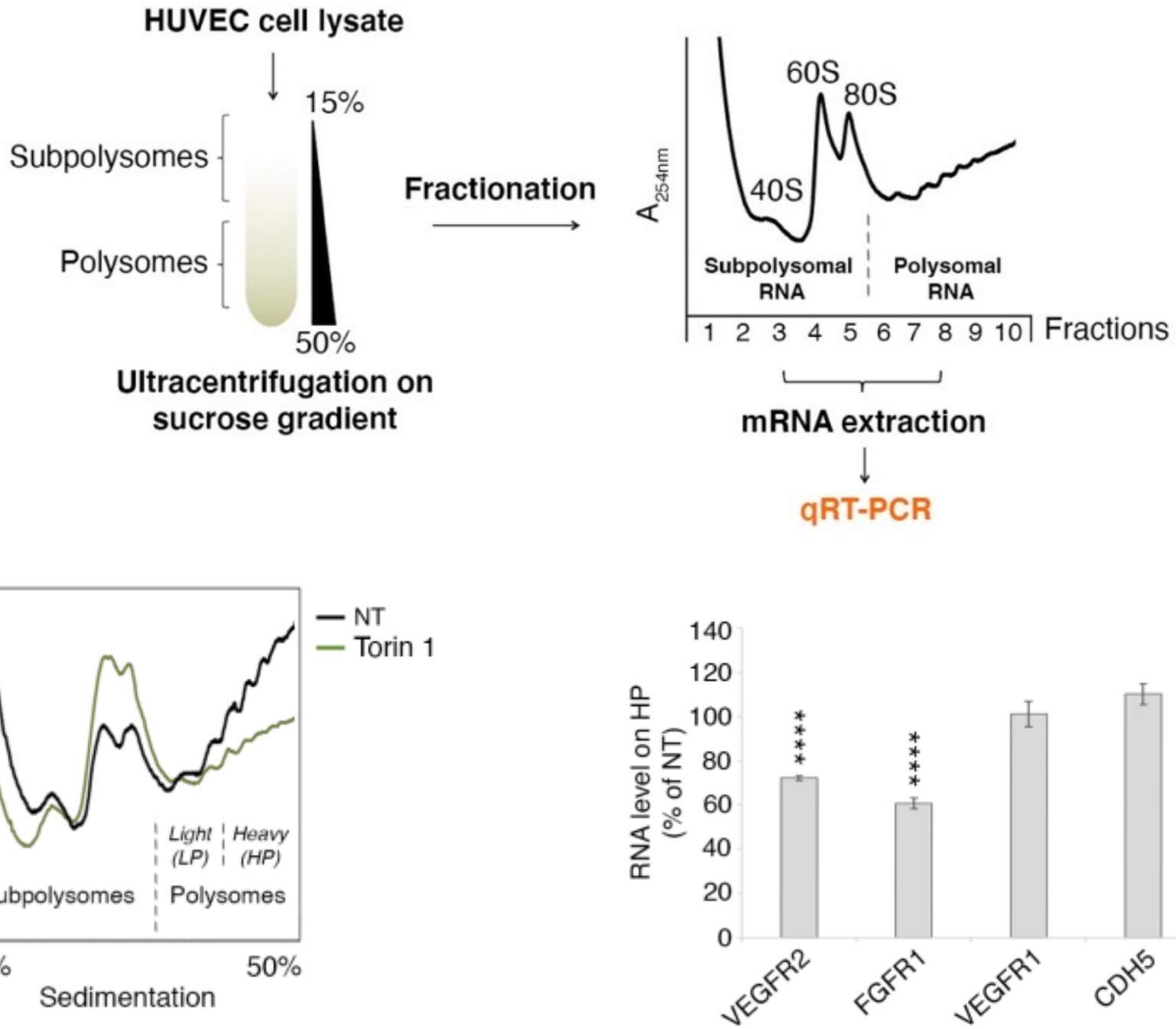
TECs

LLC1		B16F10	
*Gls1*fl/fl	*Gls1*iΔEC	*Gls1*fl/fl	*Gls1*iΔEC
VEGFR2		VEGFR2	
VE-cadherin		VE-cadherin	
P-S6		P-S6	
P-4EBP1		P-4EBP1	
β actin		β actin	

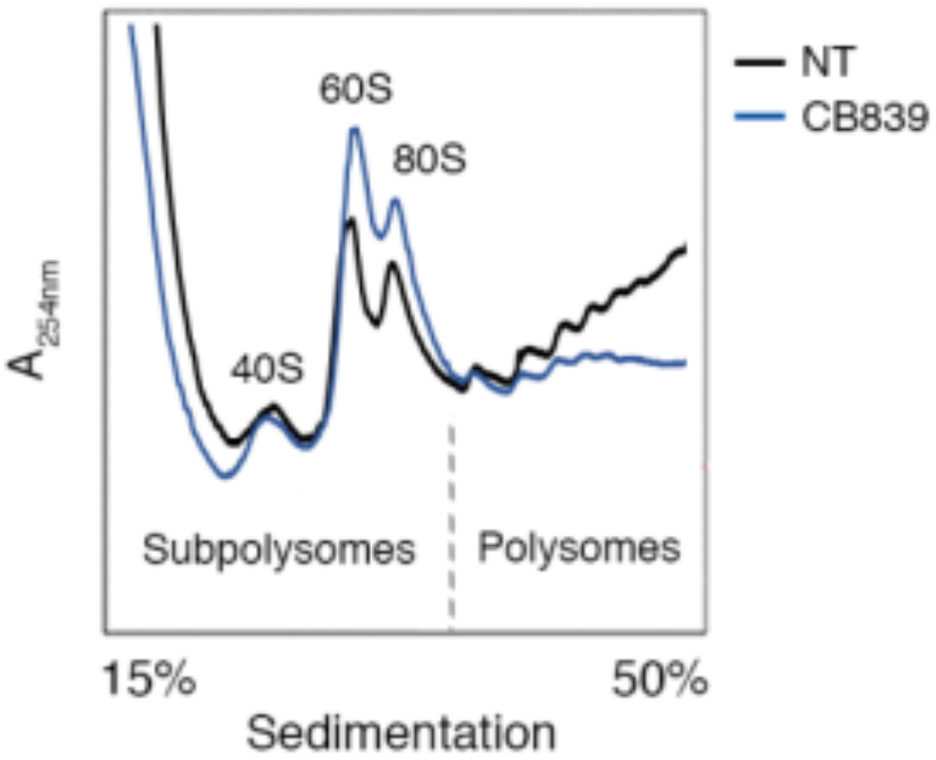
Rate of translation by polysome profiling analyses

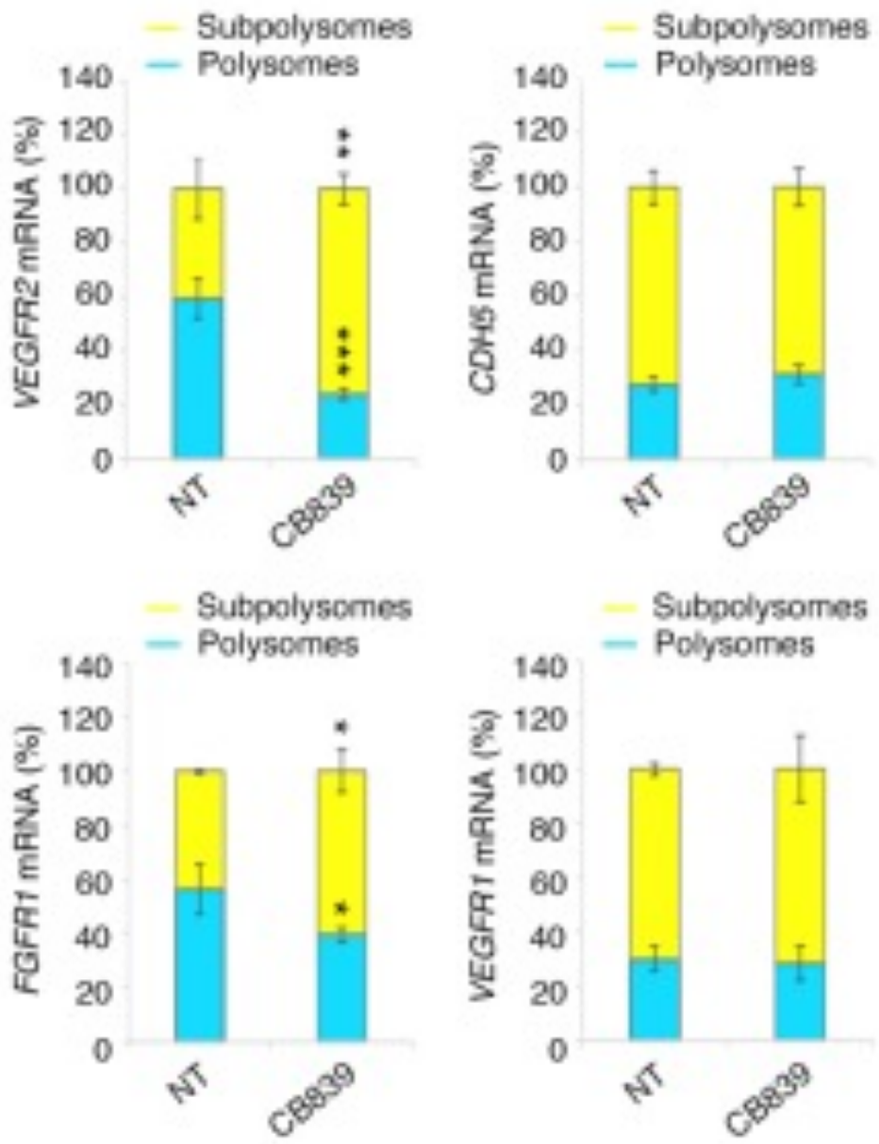


mTORC1 blockade impairs VEGFR2 and FGFR1, but not VEGFR1 or CDH5 mRNA translation

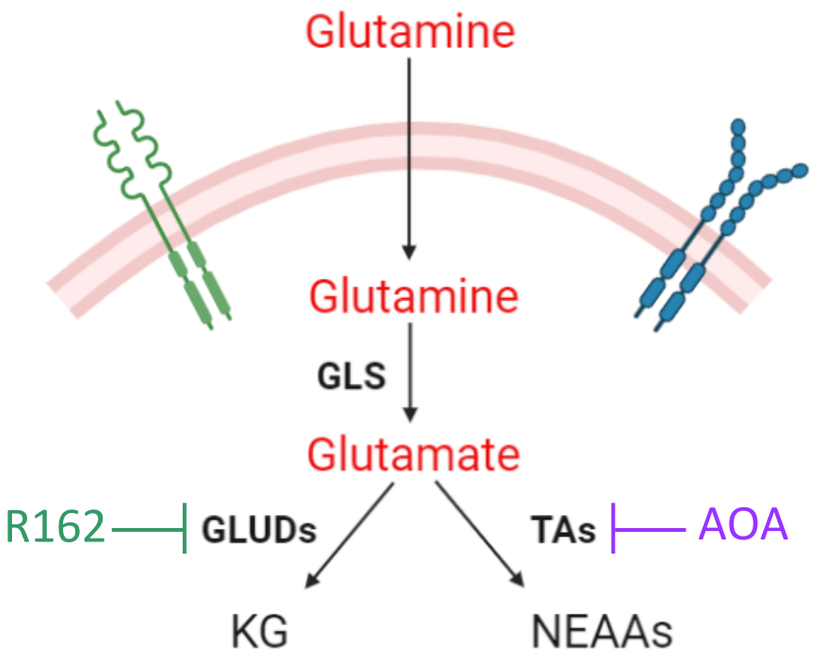


Glutaminolysis blockade impairs VEGFR2 and FGFR1 mRNA translation

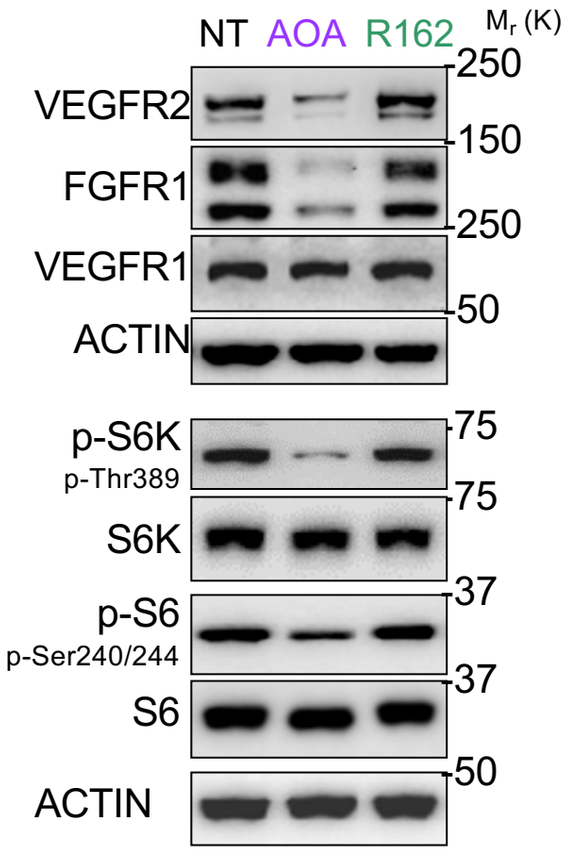


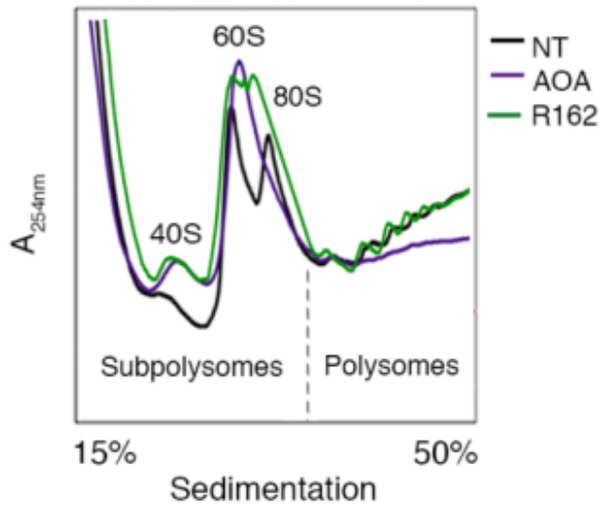


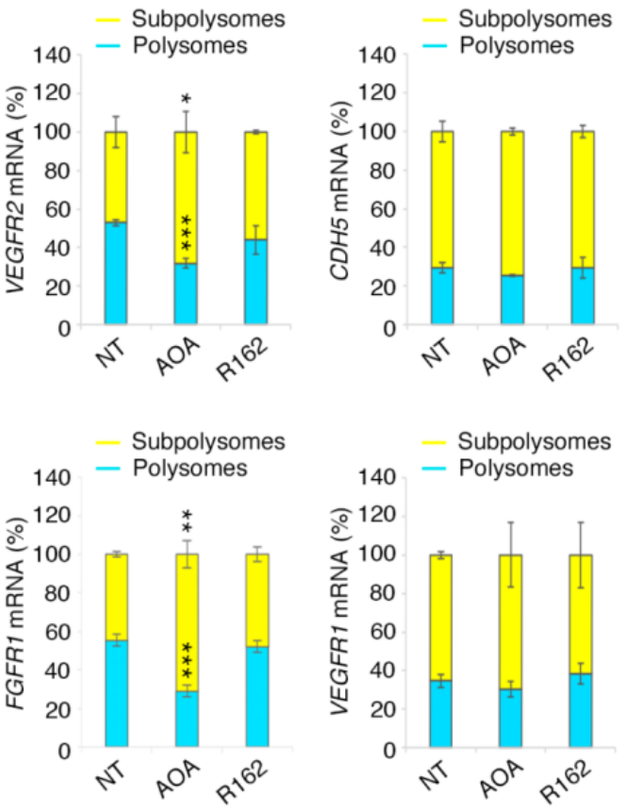
Transaminases (TAs) inhibition impairs VEGFR2 and FGFR1 translation



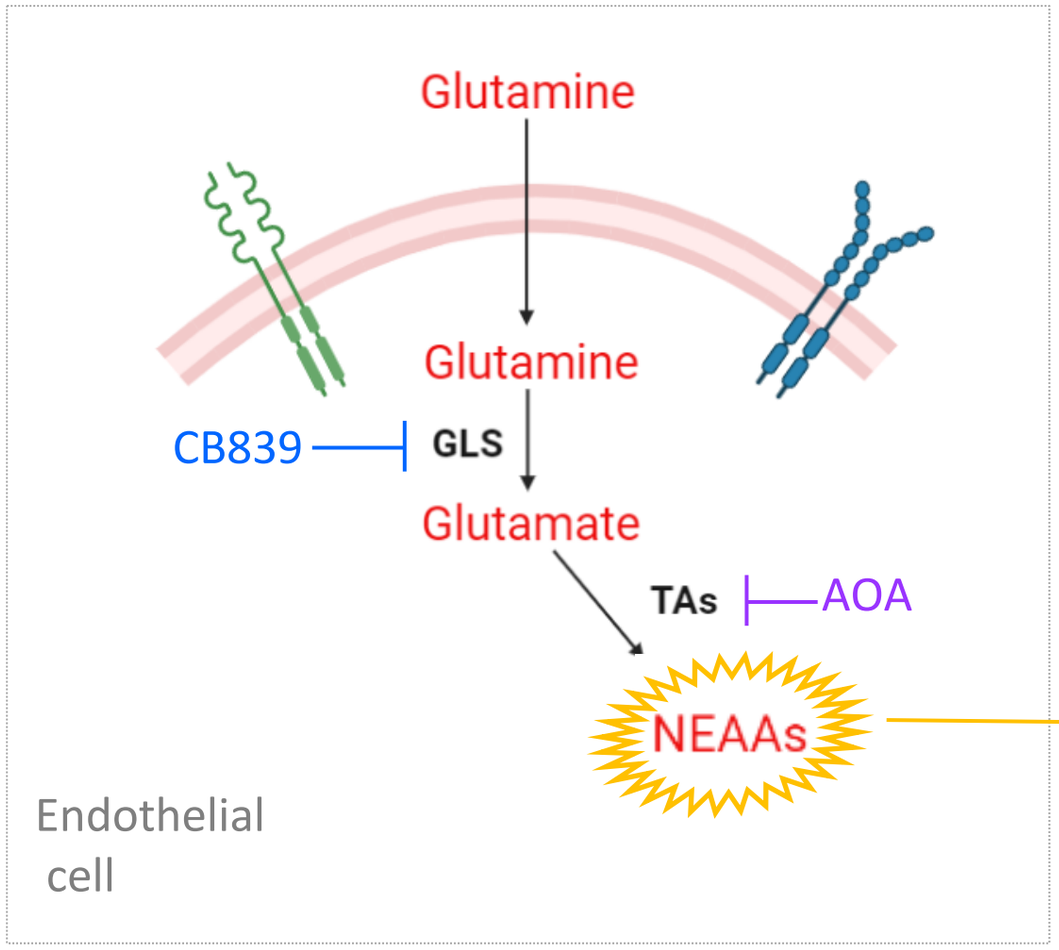
Endothelial cell

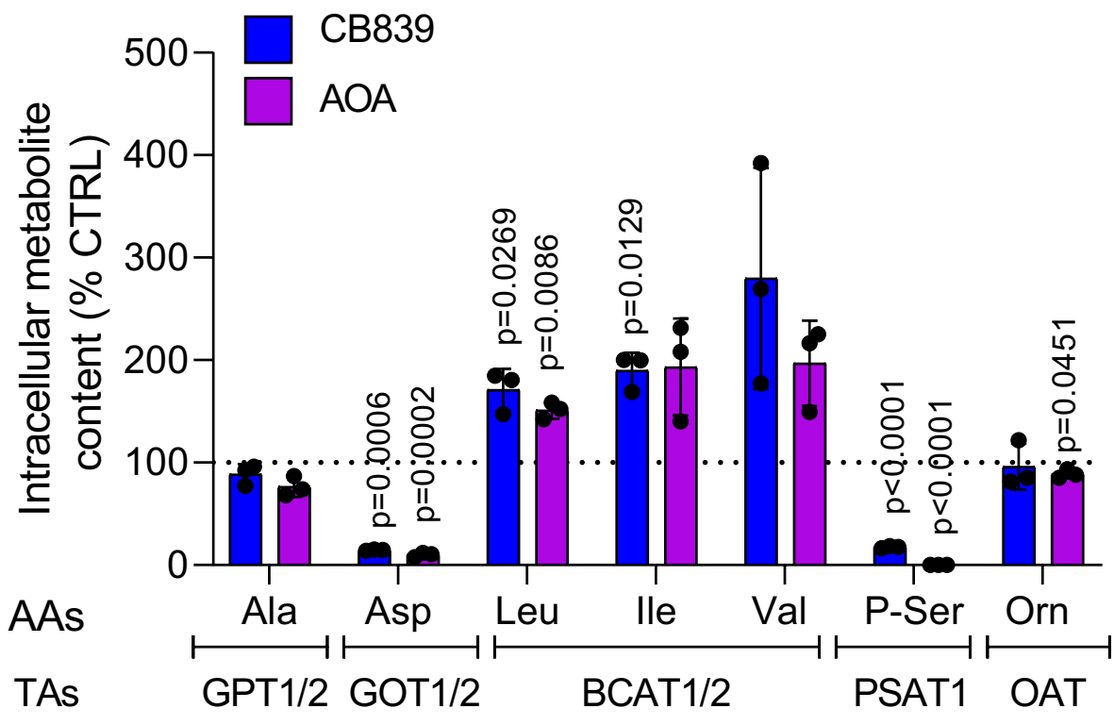




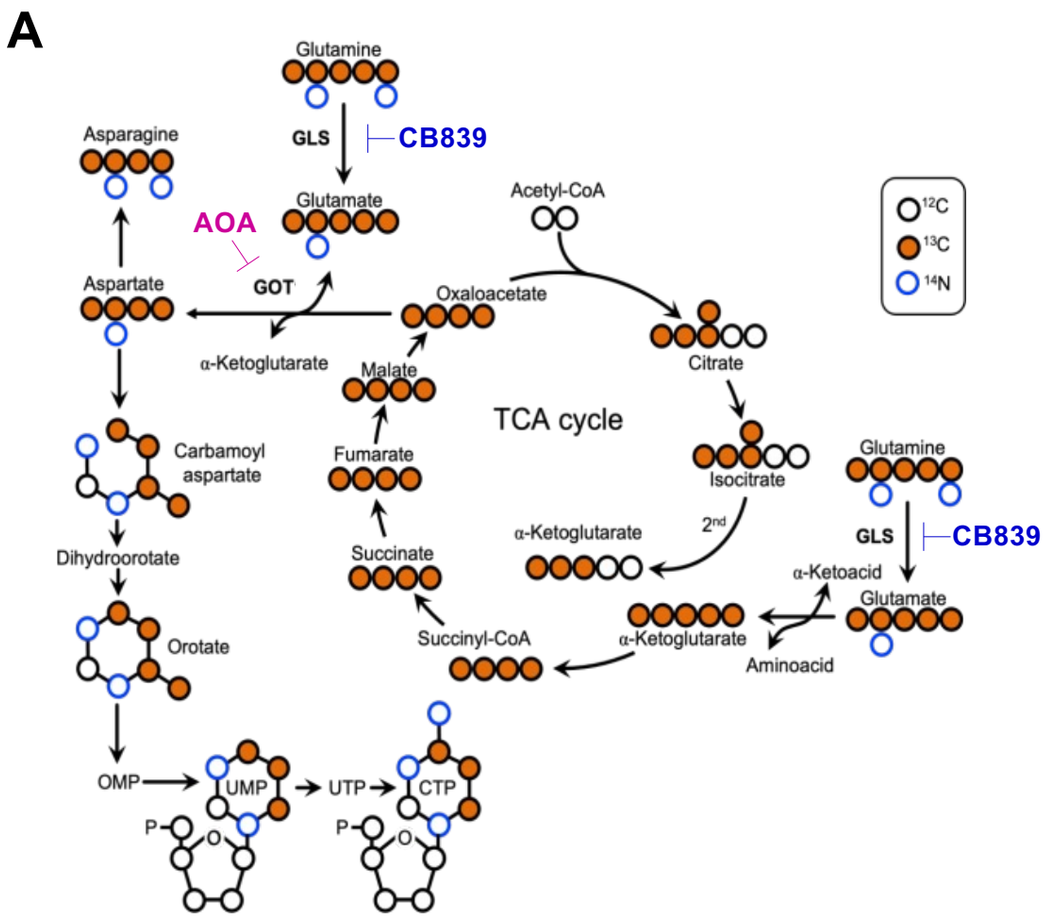


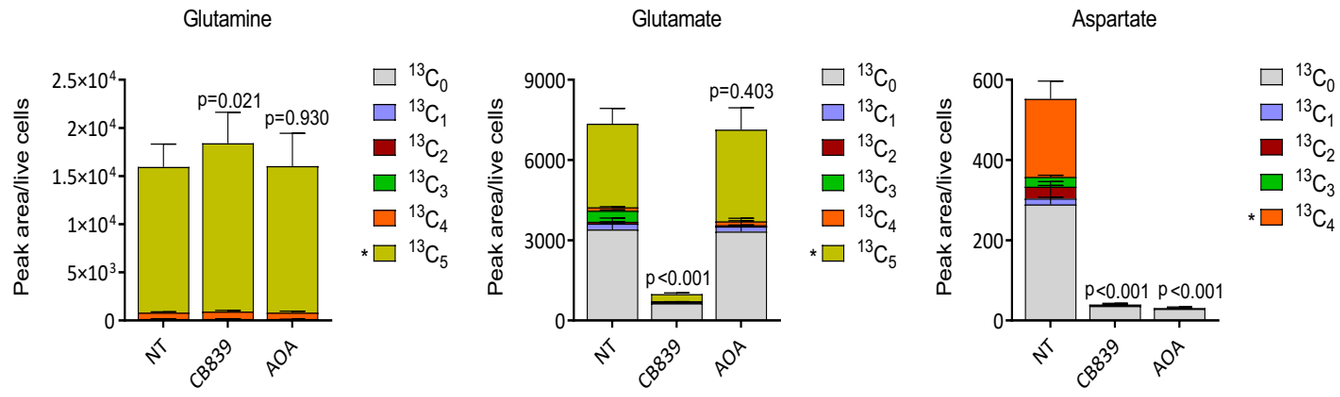
Aspartate (Asp) drops during both glutaminolysis and transamination blockade



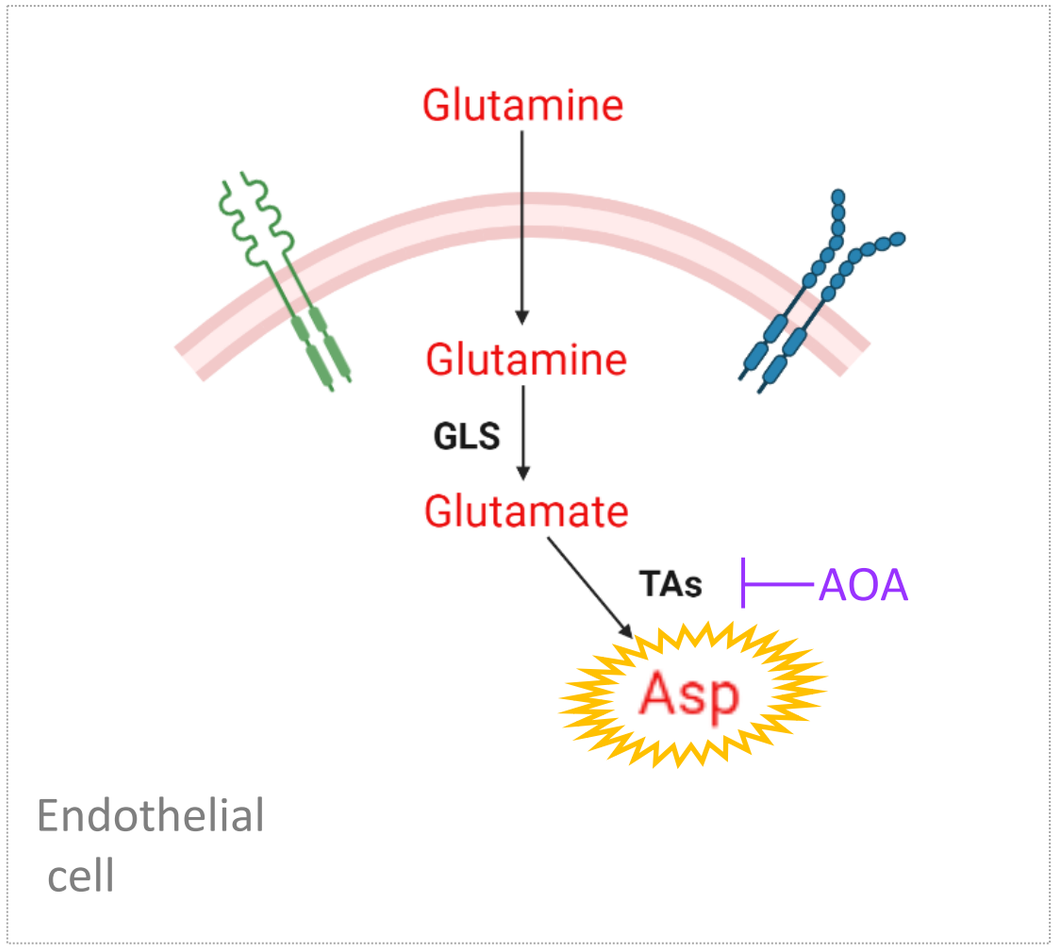


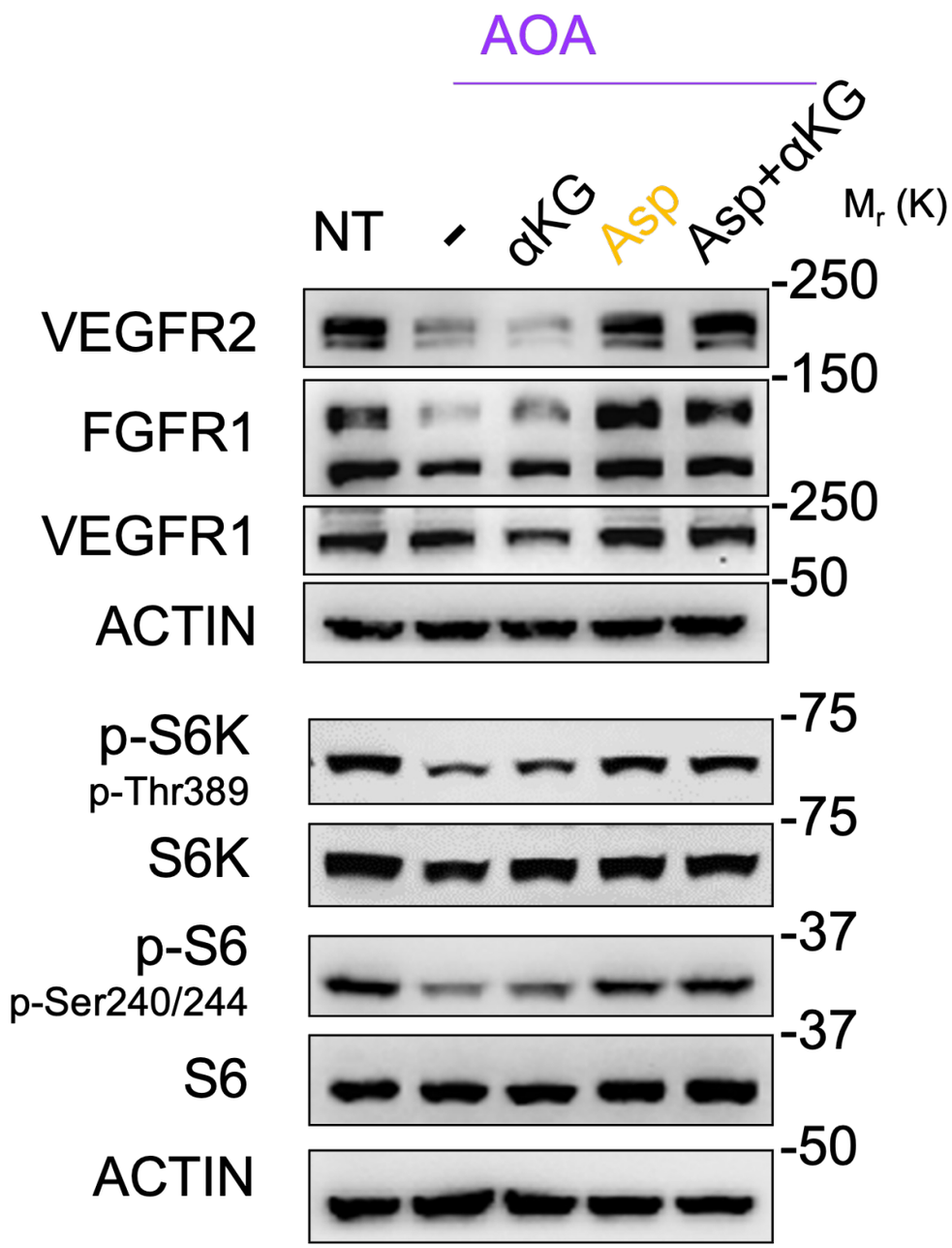
Glutamine-derived aspartate drops during both glutaminolysis and transamination blockade





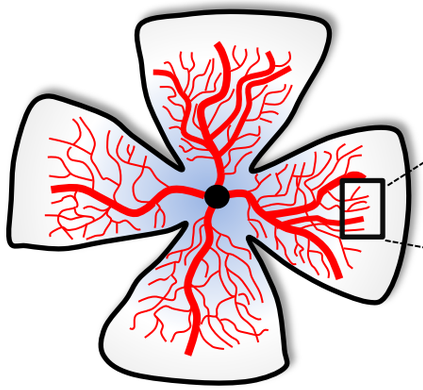
Aspartate (Asp) rescues translation and mTORC1 activation upon TAs inhibition



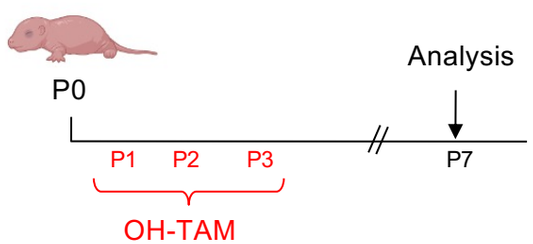


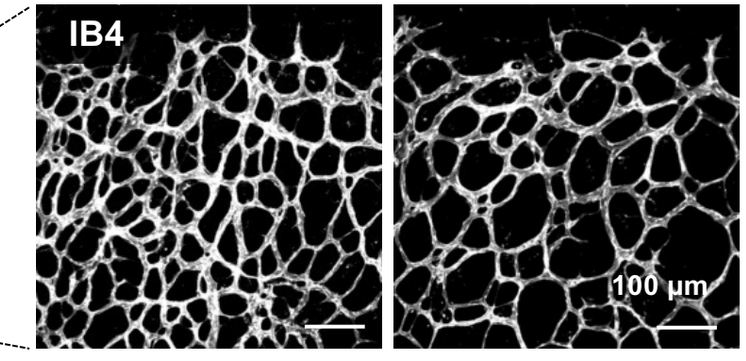
Endothelial glutaminolysis drives mTORC activation in retina angiogenesis

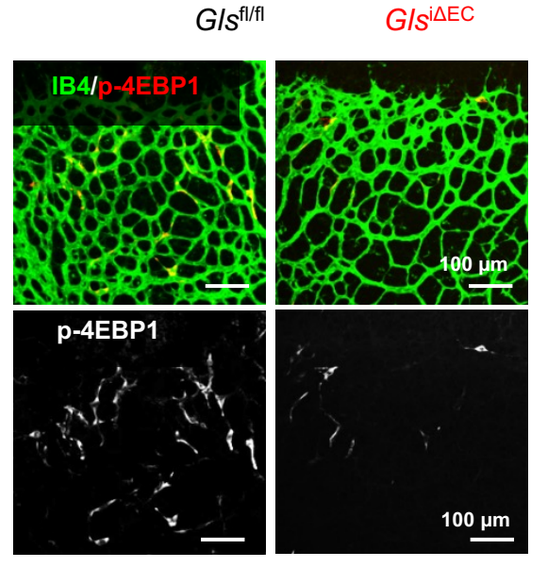
Retina angiogenesis model

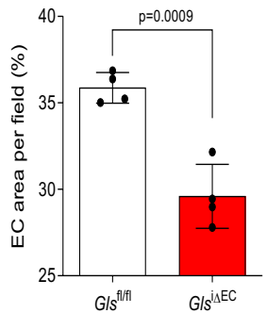


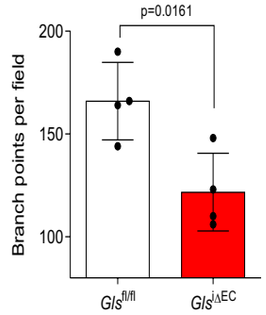
Gls$^{fl/fl}$; *PdgfbiCreERT2+*

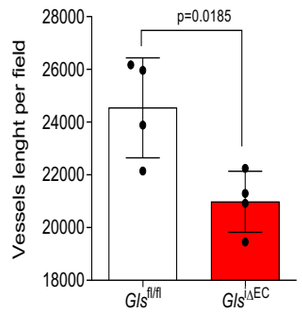


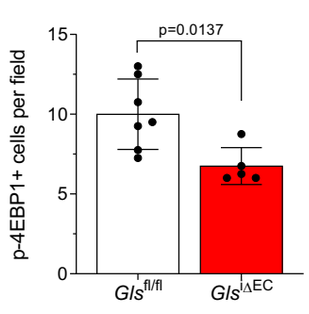








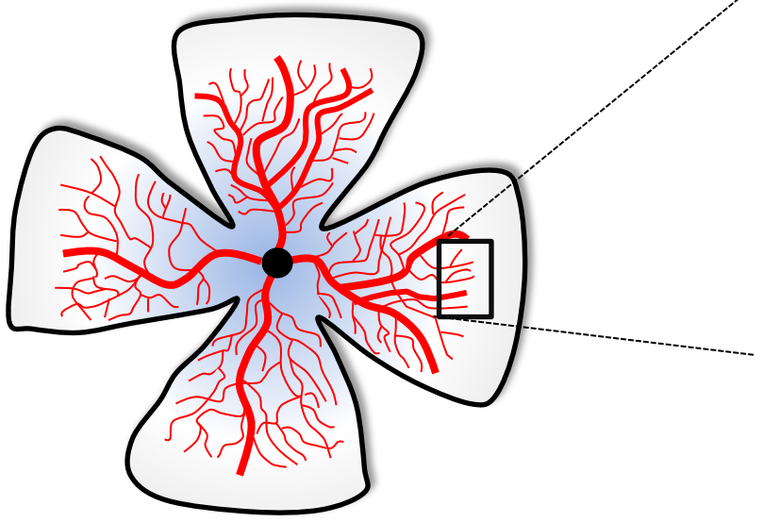




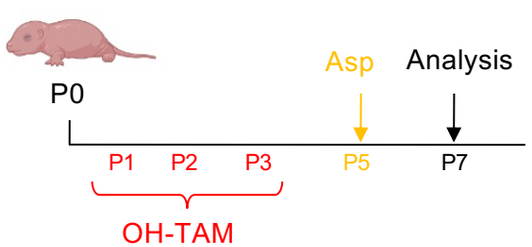
Aspartate rescues glutaminolysis blockade in retinal angiogenesis

A

Retina angiogenesis model



Gls$^{fl/fl}$; *PdgfbiCreERT2+*



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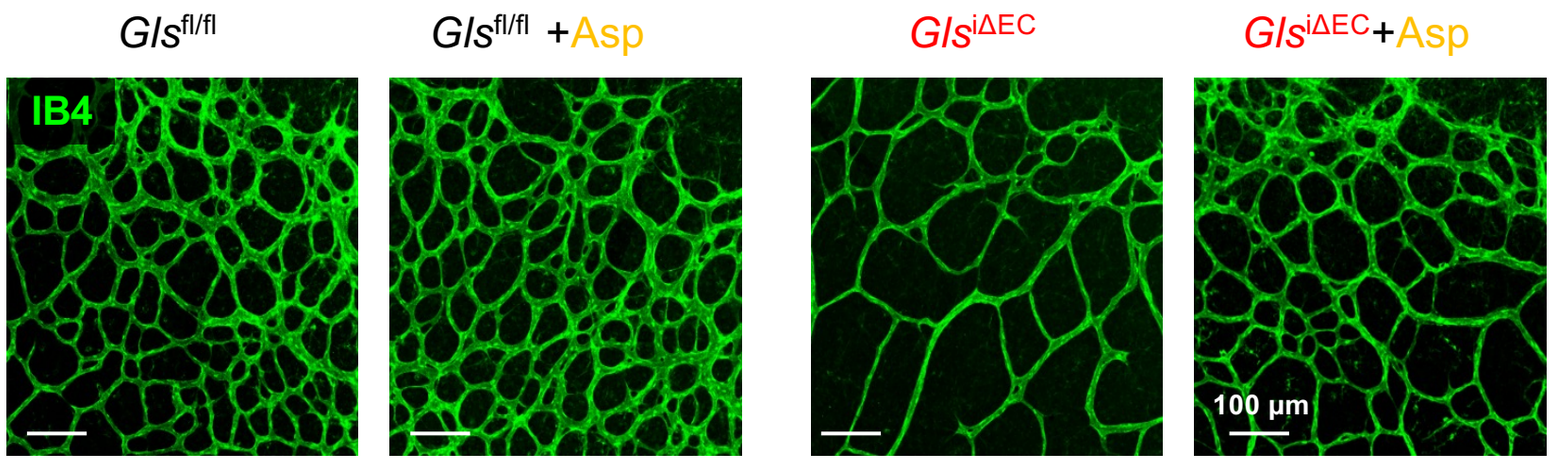
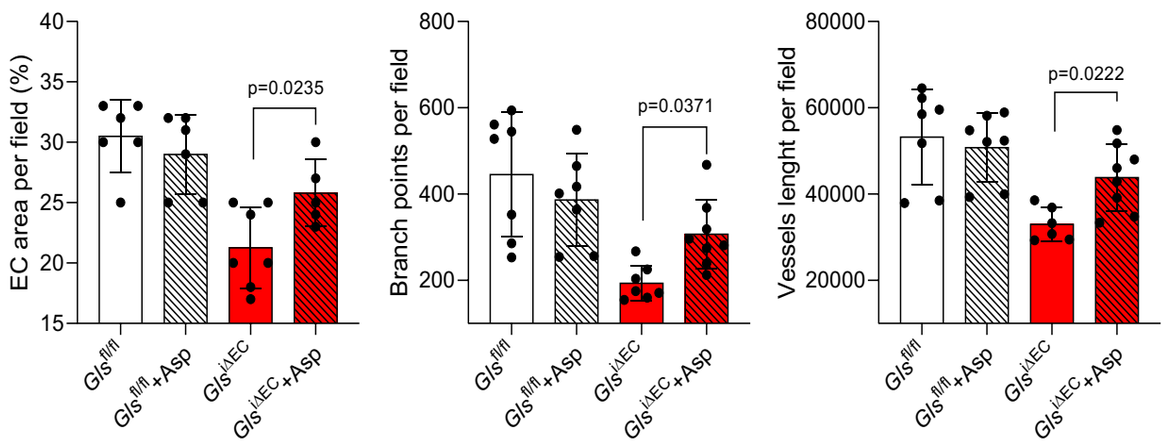
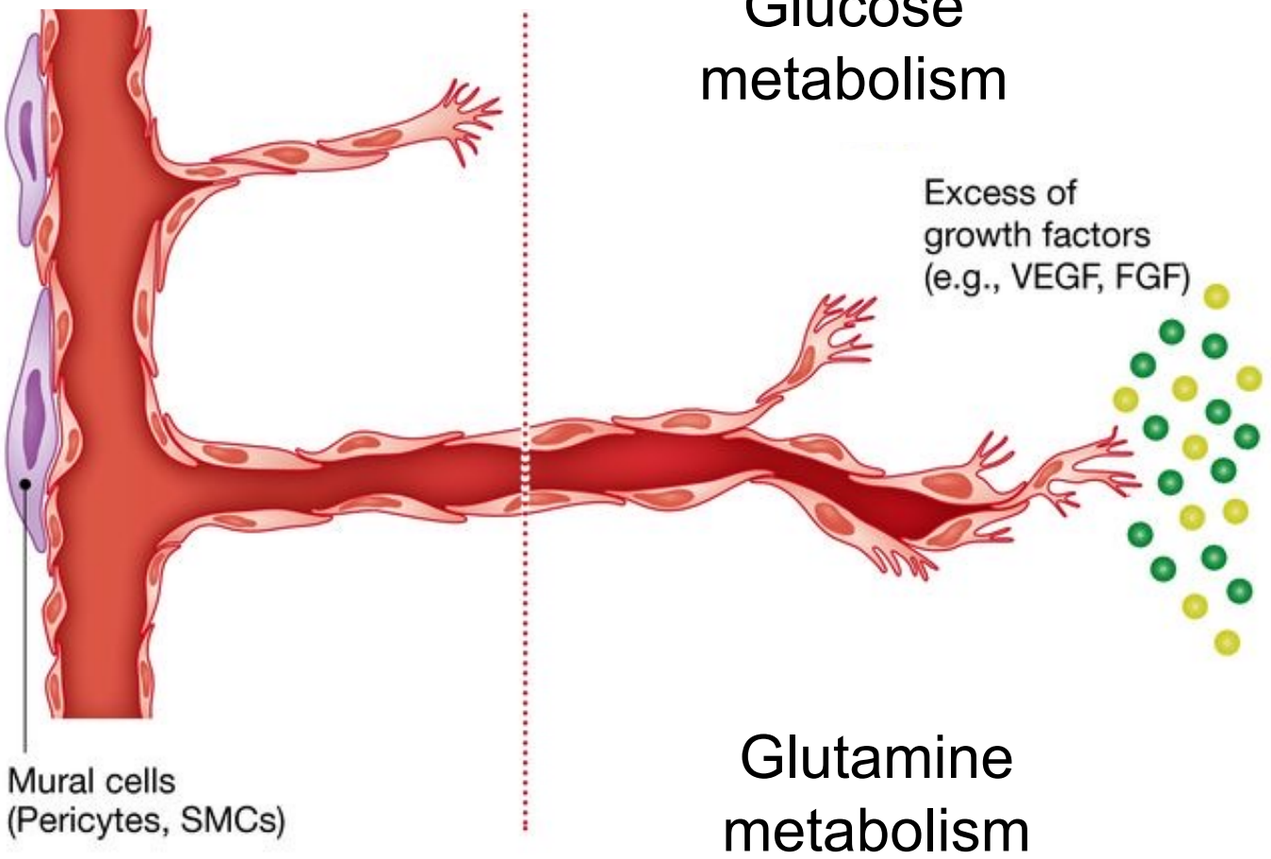




Glutamine metabolism is critical in tumor endothelial cells

ATP/energy

Glucose metabolism



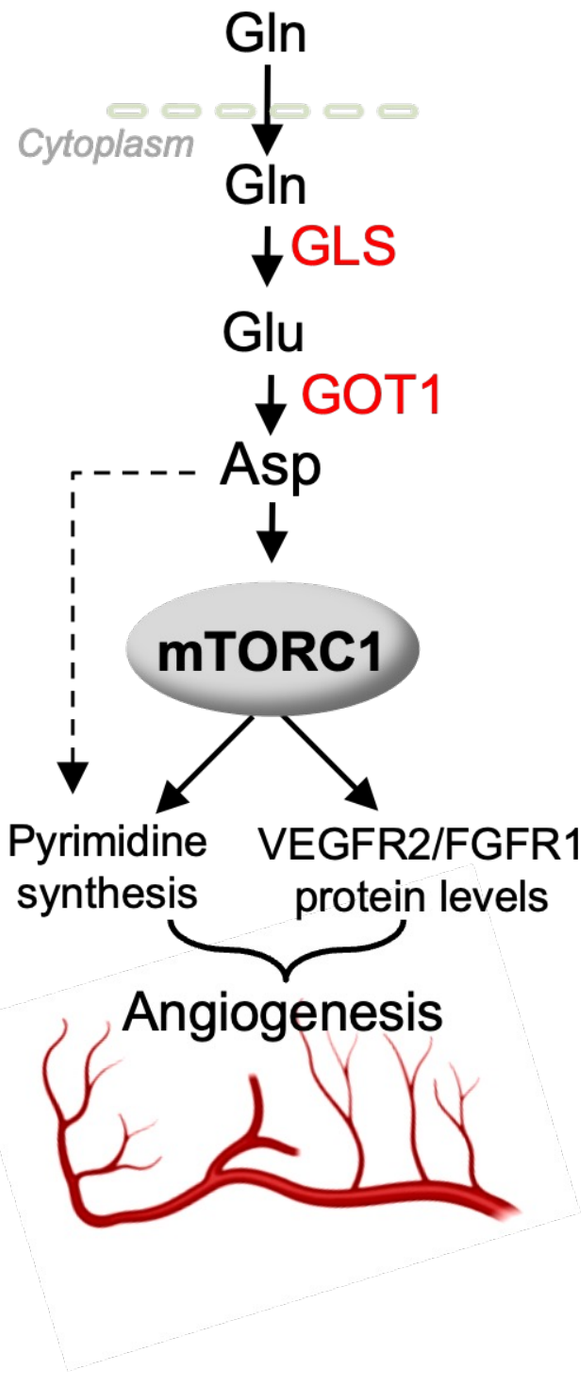
Glutamine metabolism

Hypoxic solid tumor

VEGFR2/growth factor response

Conclusions

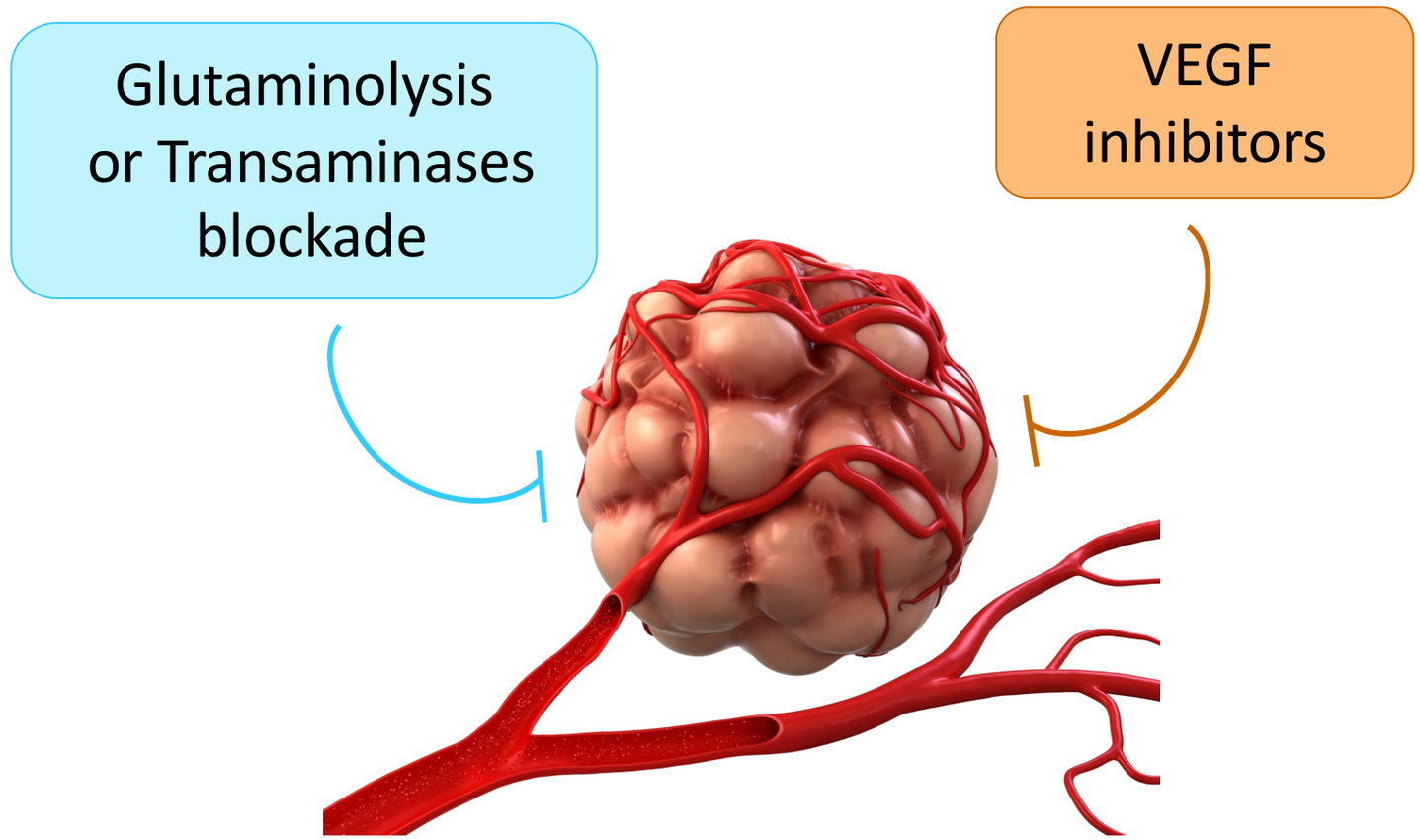
- Endothelial glutaminolysis is required during tumor and ischemic angiogenesis.
- Transaminases couple glutamine-derived carbons to aspartate synthesis in EC.
- mTORC1 activation is driven by glutamate and aspartate metabolism in EC.
- mTORC1-activation leads to control of endothelial growth factor receptor translation.



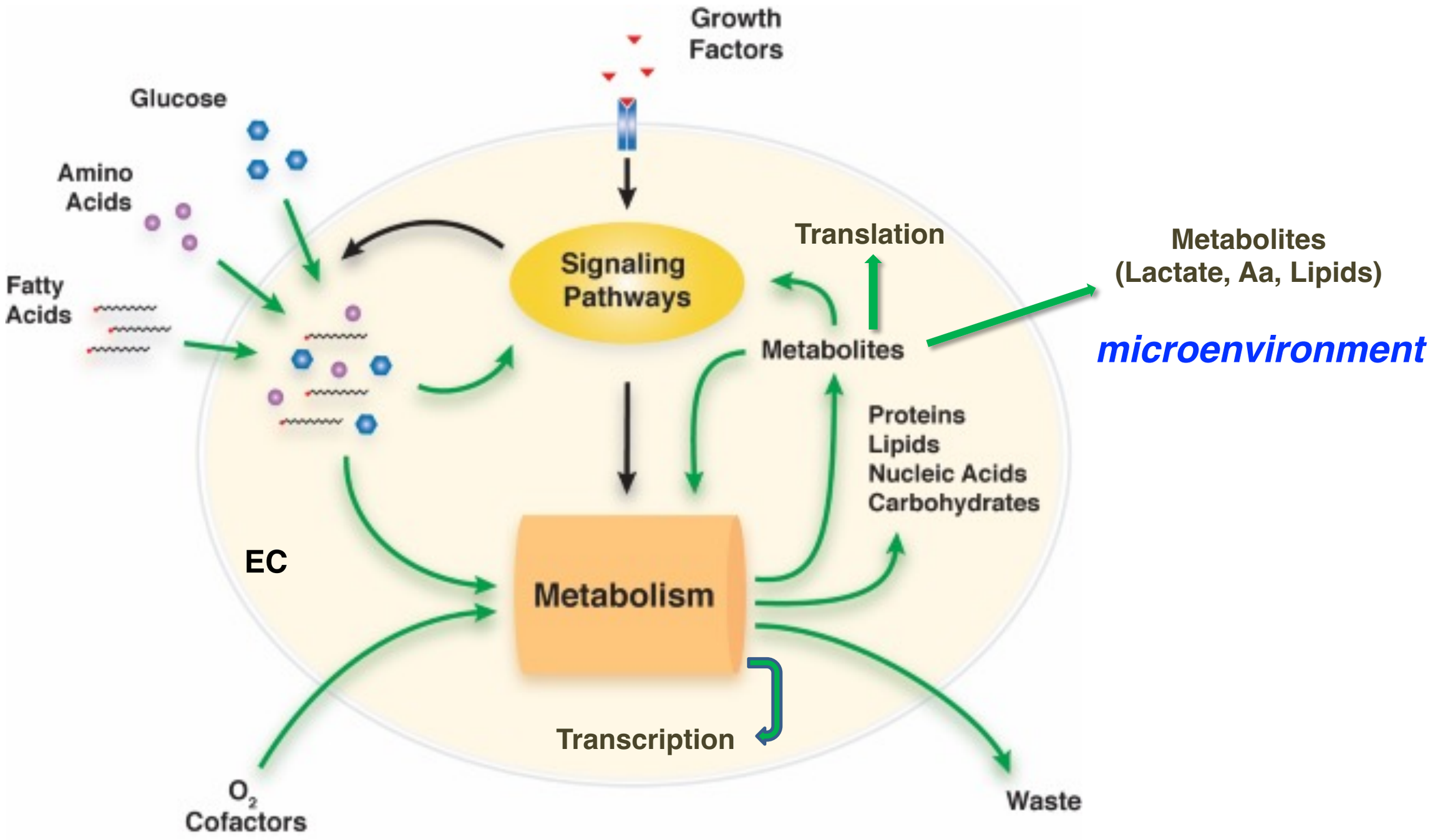
Oberkersch et al., 2022, Developmental Cell 57, 1–16
May 23, 2022
https://doi.org/10.1016/j.devcel.2022.04.018

Future perspectives

1. Dissect the translational control mechanisms in angiogenesis by translatome analyses.
2. Decode the metabolic role of GOT1 and GOT2 transaminases in ECs.
3. Evaluate a combined therapy consisting of glutaminolysis or transaminases blockade plus VEGF inhibitors that may provide a new avenue in anti-angiogenic resistance.

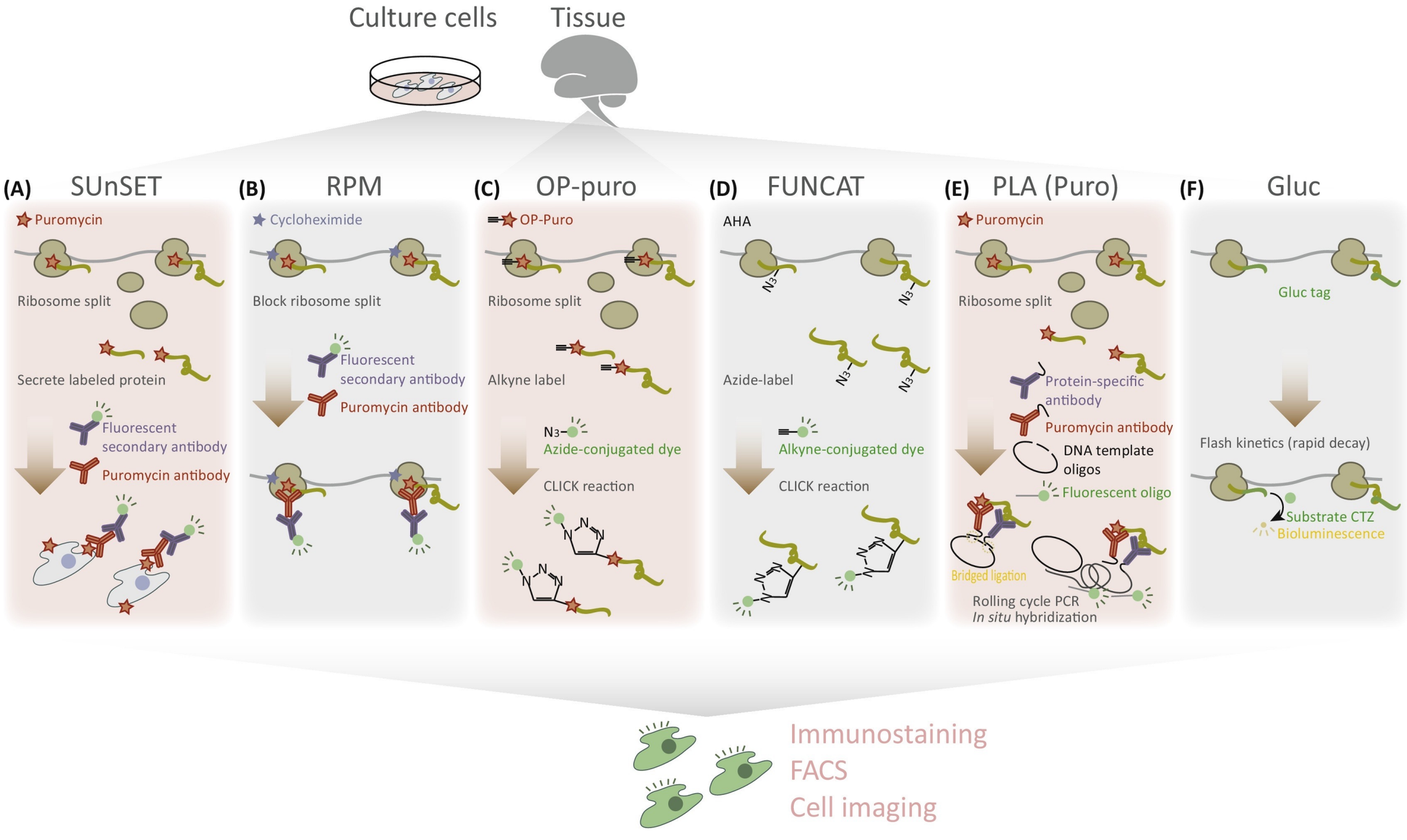


Take home message



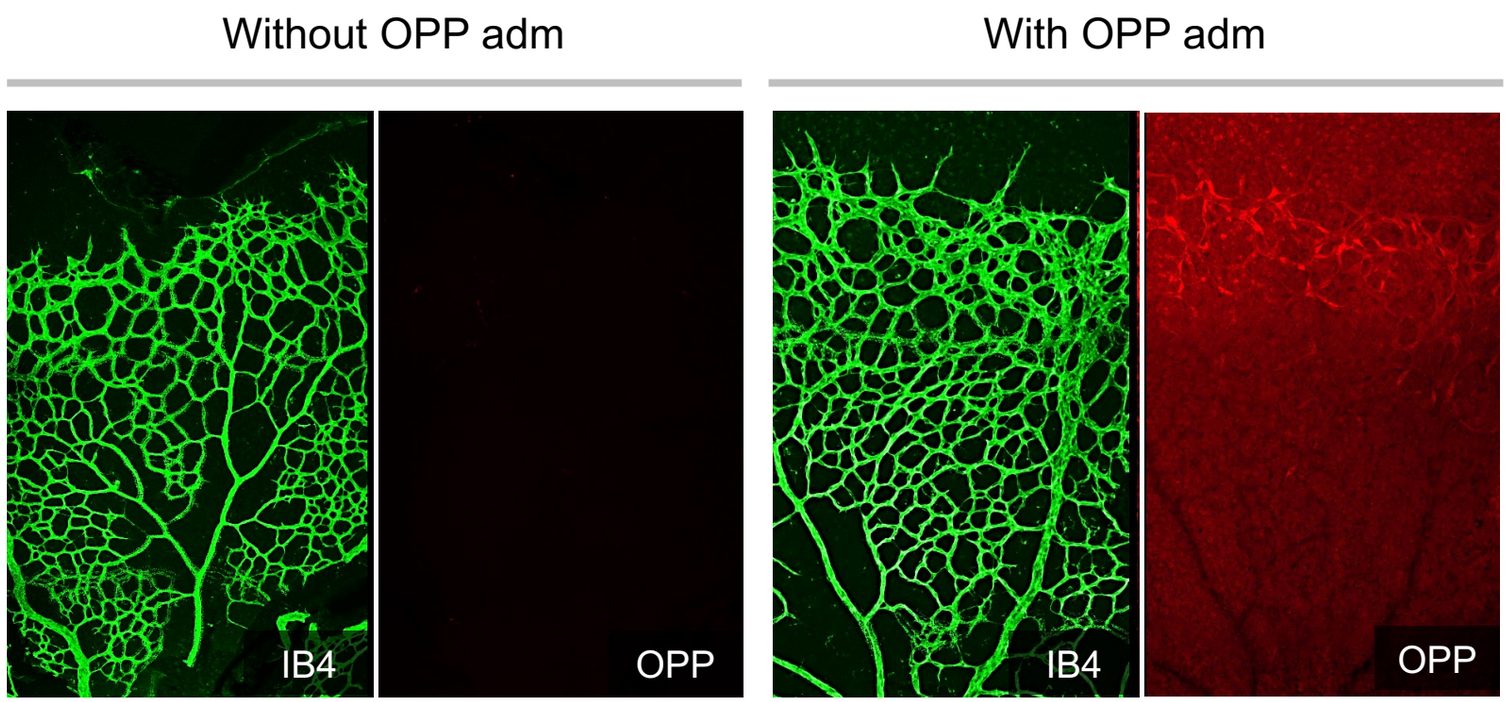
Can we study mRNA translation during
in vivo angiogenesis ?

Methods for Translation Measurement Based on Luminescent Labeling of Newly Produced Peptides



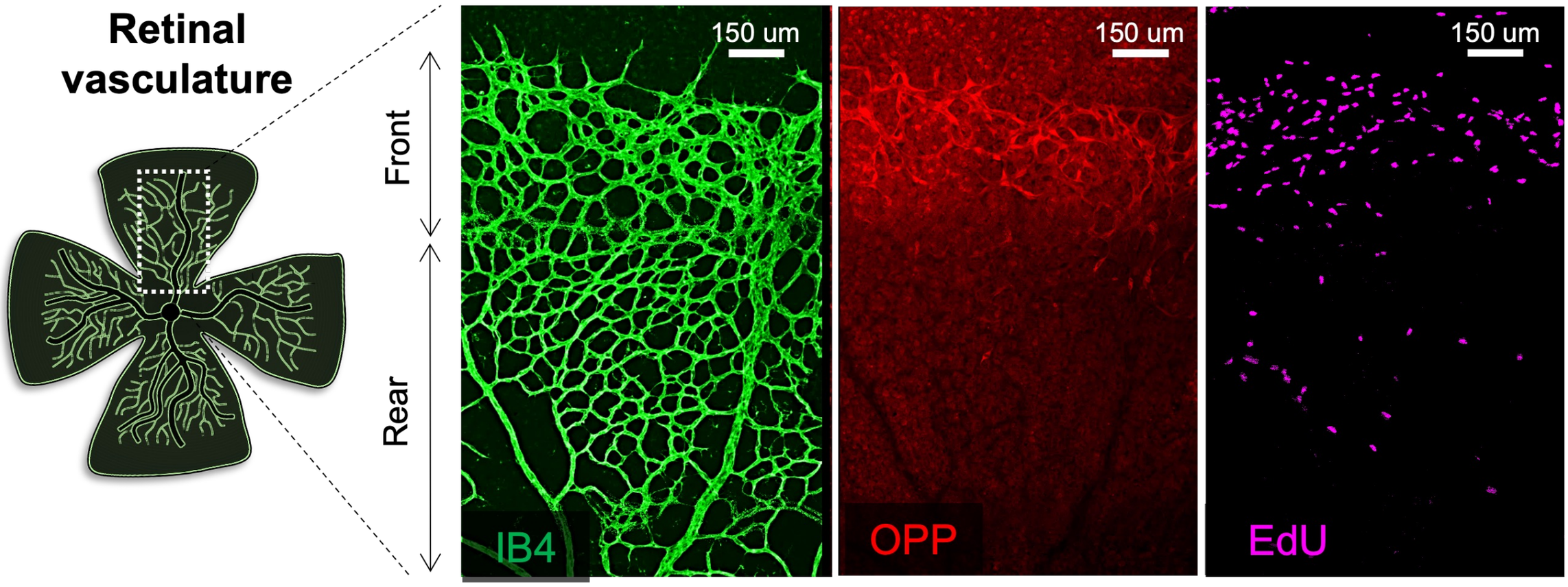
Iwasaki and Ingolia, 2017

Active translation in retinal angiogenesis



unpublished

Active Translation during angiogenic sprouting



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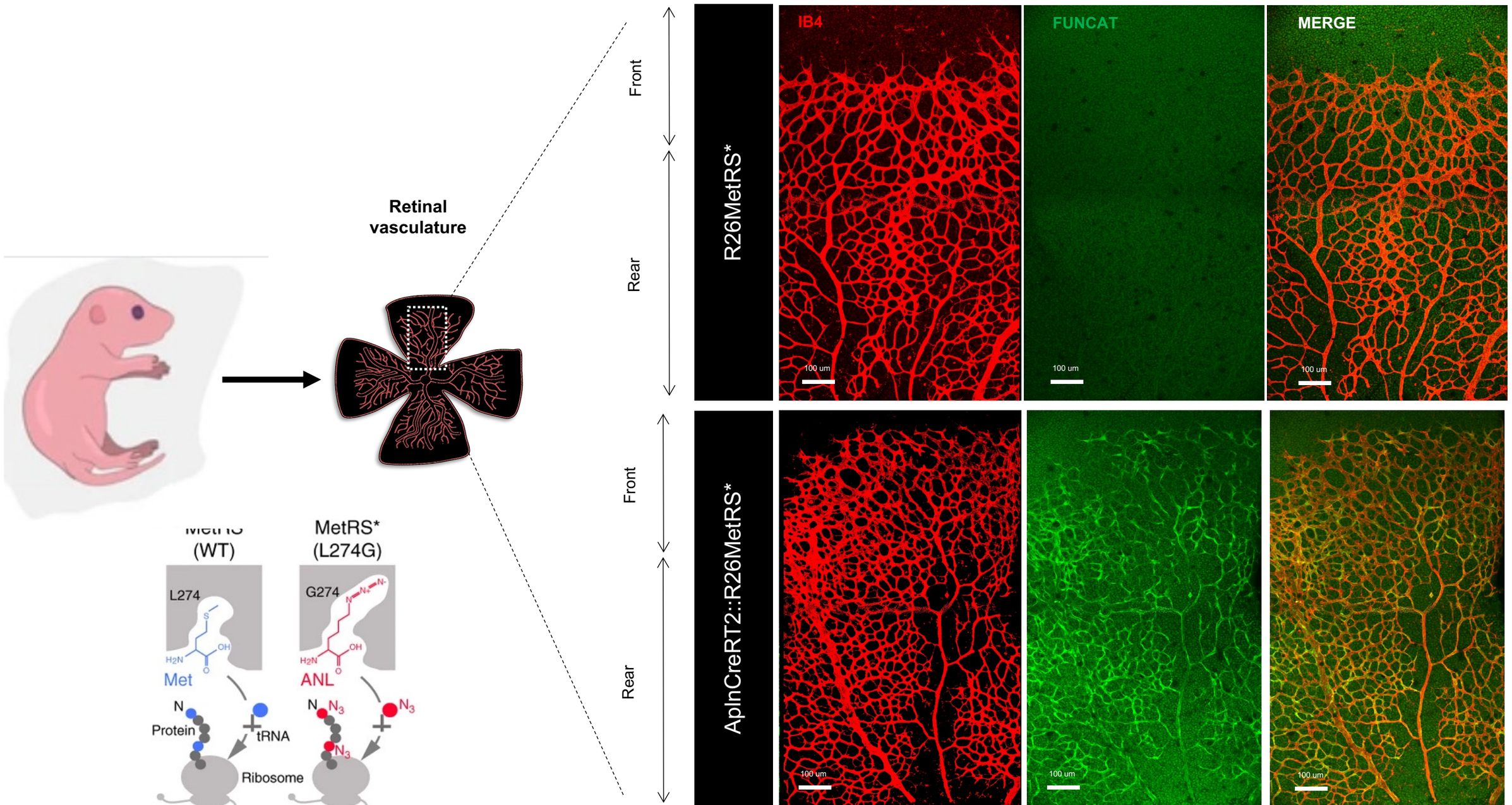
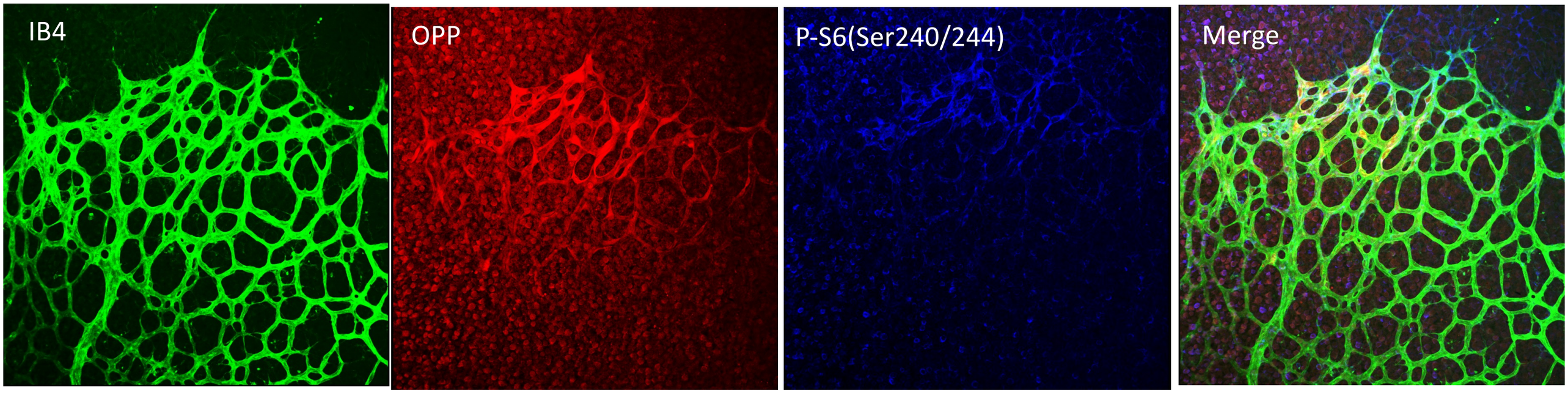
MetRS



ANL Metabolic labeling → FUNCAT

mTORC1 pathway controls translation during retinal angiogenesis



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