

Lecture 29

Sunday, July 18, 2021

00:14

mTOR part 2

- Growth signals --> mTORC1
 - o --> translation (proteins)
 - o --> DNA/RNA (nucleic acids)
 - o --> lipogenesis [metabolic formation of fat] (lipids)
- If you understand how mTORC1 works, you can interact with it to improve overall protein and cellular growth
 - o EVERYONE CAN DO IT
- Want to balance a budget
 - o Protein synthesis and ATP consumption is super energy expensive
- Function isn't possible without metabolic regulation
 - o May be a sloppy mess but is so well regulated
 - o Well-regulated because otherwise you would anabolize yourself to death
 - Destruction of regulation of mTOR signaling = death
- mTORC1 specifically contains RAPTOR and PRAS40
 - o RAPTOR is super important [regulatory associated protein of target of rapamycin]
- mTORC2 contains RICTOR, MSIN1, and PROTOR
 - o RICTOR is rapamycin-insensitive companion of target of rapamycin
- mTORC1 is downstream of mTORC2
- mTORC1 is the most critical regulator of skeletal muscle metabolism (protein synthesis and degradation) -- will focus mainly on complex 1
 - o Complex 2 is more about promoting stress responses necessary for cell survival
- mTOR complex 1 - protein synthesis is downstream from mTOR
 - o mTOR enzyme
 - o Raptor (regulatory associated protein of target of rapamycin)
 - Regulatory associated protein of mTOR - functions as a scaffolding protein that facilitates the recruitment of

substrates to the mTOR kinase [primary function: recruiting the downstream targets (substrates) for mTOR so it can actually phosphorylate the downstream targets]

- Very abundant in skeletal muscle
- Huge point of interaction/communication
 - Tuberin as well
- Can be phosphorylated on multiple sites
- MAPK super anabolic (promotes RAPTOR) [phosphorylates raptor positively]; AMPK [phosphorylates raptor negatively] super catabolic (phosphorylates RAPTOR and inhibits RAPTOR)
- RRSK is an MAPK-activated kinase that promotes mTOR signaling
- Tuberin is inhibiting rheb which turns on mTOR
- MLST8 (GBL)
 - Lose regulation and cancer can run rampant
 - But knock out GBL and not much happens
 - Very slight and modest decrease in mTOR's phosphorylation of P70S6K
- TSC1/2 - withholds Rheb's activation
- Rheb - promotes raptor phosphorylation in a positive way -- gets mTOR to start phosphorylating
 - [activator of mTOR]
- 4EBP1 - inhibiting protein translation
- P70S6K - promoting protein translation (kinase) -- phosphorylates rpS6
- rpS6
- DEPTOR - inhibitor
 - Negative regulator of mTOR
- PRAS40 - inhibitor
 - Negative regulator of mTOR
- The mTORC1 Relay Race
 - PI3K gets activated by something
 - This phosphorylates PIP2 (to PIP3)
 - PIP3 docks PKB where it is phosphorylated (activated) by PDK; PKB does a lot, one thing: inhibit the Tsc complex
 - Tsc1/2 (2 is tuberin) normally turns off Rheb by hydrolyzing its GTP; Rheb-GTP binds to mTOR, turning it on
 - mTORC1 phosphorylates P70S6K and 4E-BP1 and downstream

- mTORC1 phosphorylates p70S6K and 4E-BP1 and downstream from that eIF4G binding
- P70S6k phosphorylation positively regulates rpS6; that leads to translation of mRNAs, increasing translation capacity
- When 4E-BP1 is phosphorylated, it is deactivated, which leads to increased rates of translation initiation, increasing translational efficiency
- Translation: ribosomes synthesize protein using mRNA transcript
- Result: hypertrophy (as a result of translational capacity and efficiency)
- Different things affect mTOR
- mTOR phosphorylates p70s6k and 4E-BP1
- That promotes more (and efficient) translation
- That's hypertrophy
 - Translational capacity = number of ribosomes
 - Translational efficiency = rate of mRNA translation