

Lecture 31

Sunday, July 18, 2021 02:49

mTOR part 4

- Endocrine system
- Primary effect of testosterone is steroidal/genomic
 - o Test binds to androgen receptors in the cytoplasm; once the hormone-receptor complex is formed, it *transforms* and is then *translocated* to the nucleus
 - o Metabolic fitness and protein turnover is regulation of hypertrophy and atrophy (cell size; CELL SIGNALING)
 - o Secondary effects that are non-genomic
- Test: regulates anabolic cell signaling cascades
 - o In part, this is through the facilitation of IGF-1 signaling
 - o [insulin-like growth factor]
- Test: activates both PKB and MAPK
 - o Inhibits LKB1 (inhibiting atrophy through mTOR)
- Test and estrogen:
 - o Weight goes up and so does strength?
 - o More release of calcium (greater calcium mobilization, resulting in a greater force and/or velocity of contraction during acute changes in their concentrations)
- Estrogen: can inhibit tuberin (phosphorylates (deactivates) tuberin)
 - o Promotes LKB1 and AMPK
- Checkpoint
 - o Insulin
 - PI3K
 - o Thyroid hormone
 - PI3K
 - o hGH/IGF
 - PI3K (mostly)
 - MAPK
 - JAK-STAT
 - o Testosterone
 - Ca²⁺-dependent MAPK activation

- Increased IGF signaling
 - Inhibition of LKB1
 - Estrogen
 - Inhibition of tuberlin
 - Promotion of Rheb
 - Promotion of LKB1 and AMPK
- What we know so far:
 - Immune/chemicals
 - As tissues are damaged/broken down, they release chemicals
 - Those chemicals can initiate hypertrophic cell signaling
 - Mechanical tension
 - Mechanical signals are created when a muscle resists a load
 - These signals are converted to chemicals; this is called "mechanotransduction" and it can initiate hypertrophic cell signaling
 - Mostly integrins, titin, and cadherins
 - Works through lots of pathways (PI3K, MAPK, DGK-PA, SAC, probably more)
 - Endocrine system
 - Depending on your exercise stress, several hormones can be secreted which affect protein turnover in different ways
 - Insulin, IGF/MGF, thyroid hormones (T3, T4), hGH, testosterone, estrogen
 - Aside from steroid hormone effects, works through PI3K pathway
- Nutrition
 - How are we sensing amino acids and how are they getting into the cell?
 - Within the cytosol, amino acid detection and mTOR activation involves a quadruple negative
 - Rags localize mTORC1 to the lysosome
 - GATOR1 is inhibiting those Rags
 - GATOR2 is inhibiting that
 - Sestrin2 and CASTOR1 inhibit that
 - Leucine and arginine inhibit those
- mTOR can be activated by:
 - Eat

o Ions

- Lipids (e.g. prostaglandins and phosphatic acid) have stimulatory roles
- Diets rich in cholesterol elicit elevations in circulating steroid hormones
- Androgens and estrogens have secondary effects on mTOR signaling

o Carbs

- Glycogen can bind (inhibitory) to beta subunits on AMPK
- Carb ingestion increases blood glucose
- Insulin response stimulates PI3K

o Proteins

- Cell is capable of recognizing intracellular amino acids (AAs)
- Leucine is the most significant
- Lysine and arginine are important AA's as well
- Signals through vps34 and especially Rag GTPases
- These are proteins that attach to raptor and cause the movement of the mTOR complex to the lysosome, which facilitates interaction with Rheb; mTOR and Rheb dissociate without presence of AA's