

# Lecture 31

Sunday, July 18, 2021

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## 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
    - Ca<sup>2+</sup>-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 fats

- 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