

## mTOR Part 4 of 7

### Recap:

Insulin, PI3K, PIP3, PDK, PKB, TSC1/2, Rheb, mTORC1, P70S6K, S6K,  
= protein synthesis

### What activates mTOR?

- >Chemicals
- >Mechanical Tension
- >Endocrine
- >Nutrition

### Endocrine

- >Testosterone: Primary effect is steroidal/genomic
  - Testosterone binds to androgen receptors in the cytoplasm, then is transformed and translocated to the nucleus for gene expression
  - Non-genomic actions of testosterone; regulates anabolic cell signaling cascade
  - Testosterone activates both PKB and MAPK
  - Testosterone inhibits atrophy through mTOR (LKB1)
- >Estrogen: Primary effect is steroidal/genomic
  - Able to enhance myosin and actin binding processes due to modulations in calcium mobilization.
    - Increase in intracellular calcium
    - Estrogen can inhibit tuberlin (TSC2)
    - Estrogen promotes LKB1 and AMPK
- >Insulin & IGF1 (Insulin-like growth factor)
  - Mobilizes glucose to enter the cell for mTOR
- >Growth hormone
  - Hipo-thalamic-liver axis
  - JAK/STAT
  - Main road: PI3K, PKB

### Recap:

Insulin: PI3K  
Thyroid hormone: PI3K  
hGH/IGF: PI3K, MAPK, JAK-STAT  
Testosterone: Calcium depended MAPK, increased IGF signaling, inhibit LKB1  
Estrogen: Inhibit Tuberlin (TSC2), promote rheb, promote LKB1 and AMPK

### Immune:

As tissues are damaged, they release chemicals. Those chemicals can initiate hypertrophic cell signaling.  
ie; prostaglandins, IL-2, IL-15, interferons  $\gamma$ , ROS, Wnt, TNF $\alpha$ . Works through MAPK and PI3K pathways

### Mechanical:

Mechanical signals are created when a muscle resists 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, SAC)

### Endocrine:

Depending on your exercise stress, several hormones can be secreted, which affect protein turnover in different ways. Insulin, IGF, thyroid hormones, hGH, testosterone, and estrogen work through PI3K pathways

#### Nutrition

- amino acid sensing
  - >Leucine, lysine and arginine are more important for mTOR signaling
- SLC38A9 is a transmembrane that senses intra-lysosomal arginine

AA detection and mTOR activation require a quadruple negative:

- Rags localize mTORC1 to the lysosome
- GATOR1 is inhibiting those rags
- GATOR2 is inhibiting that
- Senstrin 2 and CASTOR 1 inhibit that
- Leucine and arginine inhibit those

LKB1(Liver kinase b1): Activates AMPK

ROS mediate the effects of leucine on translation regulation and type I collagen production in cells

#### Recap:

##### Nutrition

Fats: Lipids have stimulatory roles. Diets rich in cholesterol elicit elevations in circulation steroid hormones. Androgens and estrogens have secondary effects on mTOR signaling

Carbs: Glycogen can bind (inhibitory) to beta subunits on AMPK; carb ingestion increases blood glucose; insulin response stimulates PI3K

Proteins: The cell is capable of recognizing intracellular AA. Leucine is the most significant, Lysine and arginine are important AAs too. Signals through VPS34 and 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 the presence of AA.

Review: mTOR is activated by:

If you're using a cell (Hennemans size principle) you may need to repair that cell and you may need to reinforce it against future damage from the same stress.

When a cell is damaged, you get an inflammatory response. Immune chemicals function as a marker for the magnitude of damage necessary for repair. They provide signal for architectural disruption and initiate repair (PKB and MAPK). Mechanical loads are also transmitted to demonstrate what this cell is doing now.. because what you're currently doing is a good indication of what you need to do in the future.

Sensing of chemical and mechanical loads: these are necessary for repair and remodeling. They don't announce nutrition coming; they announce the need.

Adequate nutrition is necessary for stimulation of growth.