Role of mTOR signaling in normal and pathological conditions

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Role of mTOR signaling in normal and pathological conditions

• Objectives:
  – Describe the role of the PI3-kinase/Akt/mTOR pathway in normal cell function.
  – Describe the role of the PI3-kinase/Akt/mTOR pathway in cancer and other diseases.
  – Discuss the role of mTOR inhibitors in clinical practice.

• Suggested Reading:
  – Laplante and Sabatini. mTOR signaling at a glance J. Cell Science 122, 3589-3594
Describe the role of the PI3-kinase/Akt/mTOR pathway in normal cell function: It’s complicated!
Maybe a little simpler…

Wood et al., ASN Neuro 2013
What is mTOR?

- Mammalian/mechanistic target of rapamycin
  - Two complexes
    - mTORC1 associates with Raptor in a complex that is “rapamycin-sensitive”
    - mTORC2 associates with Rictor in a complex that was originally assumed to be “rapamycin-insensitive”.
  - Both complexes drive many cellular processes.
  - Because of its rapamycin sensitivity, mTORC1 was discovered first and is better characterized than mTORC2.
Growth factors activate Phosphoinositide 3 kinase (PI3K) by activating PI3-kinase, which phosphorylates phosphoinositides. Phosphoinositides then activate phosphoinositide-dependent kinase 1 (PDK-1). PDK-1 phosphorylates Akt. Phosphates are removed from phosphoinositides by Phosphatase and tensin homolog (PTEN), thereby activating PDK-1 and Akt.

Wood et al., ASN Neuro 2013
Akt has many functions. Today just focuses on its impact on mTOR.

Akt phosphorylates Tuberous Sclerosis 1/2 (TSC1:Hamartin and TSC2:Tuberin) TSC1/2 phosphorylation blocks its actions.

Wood et al., ASN Neuro 2013
TSC1/2 function as a complex to downregulate mTOR activity. It phosphorylates and thereby inhibits Rheb1, which normally activates mTORC1. Note that rapamycin inhibits mTORC1, while Akt directly phosphorylates and activates it.
TSC1/2 inhibit mTORC1 activity, but increase mTORC2 activity. Note that rapamycin looks like it also inhibits mTORC2. It does, at high doses or prolonged exposure.
What do mTORC1 and mTORC2 do?

mTORC1 is highly involved with protein translation. mTORC2 regulates Akt itself and impacts the cytoskeleton.
Highly interactive signaling

mTORC2 regulates Akt activity by phosphorylating it at Ser 473, which is required for full Akt activation. Activated Akt downregulates TSC1/2 activity, thereby activating mTORC1 and directly activates mTORC1 by phosphorylation of mTOR itself. mTORC1 activates S6Kinase 1, which regulates protein synthesis. Phosphorylated S6K1 inhibits mTORC2, thereby downregulating Akt activation.
Function of the Akt/mTOR pathway

• To sense the environment
  – mTOR highly activated in the “good” conditions
    • Amino acid “sensor”
    • High ATP/AMP ratio
    • Activated by growth factors
  – Loss of mTOR activity induces autophagy in “bad” conditions
Function of mTOR

• mTOR is regulated by/and regulates metabolism
  – High nutrient state
    • High mTOR
    • Anabolism
    • Energy storage
  – Low nutrients
    • Low mTOR
    • Potentially autophagy/mitophagy to release amino acids, metabolites that feed back to mTORC1
mTORC1

- mTOR complexes with Raptor (regulatory-associated protein of mTOR).
- Nutrient sensitive
- Also activated by insulin and other growth factors in mammals.
- Activates ribosome biogenesis and protein synthesis
- Phosphorylates and inhibits repressors of mRNA translation 4E-binding proteins (4E-BPs) and activates the ribosomal S6 kinase (S6K1).
- TORC1 inhibits autophagy.
- Inactivated in stress conditions
mTORC2

mTOR complexes with Rictor (rapamycin-independent companion of TOR)

Phosphorylates Akt on Ser473 which enhances likelihood of full Akt activation by phosphorylation on Thr301.

Involved in cytoskeletal organization.
mTOR in environment with excess nutrients

• Excess mTOR activity
• Metabolic dysfunction
• Excess adipocyte differentiation into white adipose tissue.
• mTORC2 drives excess lipid biogenesis and glycogen
• Excess mTORC1 downregulates signaling from the insulin receptor—insulin insensitivity
Describe the role of the PI3-kinase/Akt/mTOR pathway in cancer and other diseases
Describe the role of the PI3-kinase/Akt/mTOR pathway in cancer

Several crucial molecules in this pathway are known tumor suppressors.

TSC1/2 and PTEN mutations are familial risk factors for cancer.

Sporadic mutation/dysregulation of PI3K, Akt or PTEN are among the most prevalent genetic changes in cancer.
- Growth factors/signals activate PI3K, which in turn activates Akt.

PTEN is a tumor suppressor that downregulates Akt activation to regulate growth.

- PTEN mutations result in uncontrolled cell growth.
- PTEN mutations are common in breast, lung and prostate cancer, head and neck squamous carcinoma.
Benign tumors result from TSC1/2 deletions

• Tsc1 and Tsc2 are tumor suppressors that normally downregulate mTOR activity.

Mutations in Tsc1/2 result in tuberous sclerosis (1:6000), a devastating developmental disease.

• Pathology in tuberous sclerosis results from uncontrolled cell growth producing hamartomas, benign tumors.

• Clinical problems: epilepsy, mental retardation, kidney failure, heart and lung disease, facial angiofibroma
Akt activation itself can be oncogenic

Loss of PTEN drives Akt signaling to mTOR

Loss of Tsc1/2 drives mTOR activation

Duplication or activating mutation of Akt can drive unregulated mTOR activation
mTOR itself may drive tumorigenesis

- By suppressing autophagy, activated mTORC1 may enhance tumorigenicity
- Autophagy may be a “tumor suppressor” activity, which limits growth.
- mTORC2 activates Akt, increasing cell proliferation
  - Rictor is required for tumor growth in PTEN-deficient mice.
Describe the role of the PI3-kinase/Akt/mTOR pathway in other diseases/conditions

• Diabetes-
  – increased mTORC1 or reduced mTORC2.

• Polycystic kidney disease-
  – increased Rheb1 activity

• Systemic erythemia lupus-
  – mTORC1 increased in immune cells

• Aging

• Neurological diseases
  – Epilepsy
  – Alzheimer’s disease
Discuss the role of mTOR inhibitors in clinical practice
Discuss the role of mTOR inhibitors in clinical practice

Rapamycin/Sirolimus

– Discovered in 1970’s from Streptomyces samples on Easter Island/Rapa Nui as an antifungal agent
– Rapidly found to have strong immunosuppressant activity.
– Rapalogs—better pharmacokinetics
  • Everolimus
  • Temsirolimus
  • Deforolimus
Major mTOR inhibitors

- **Rapamycin/Rapalogs**
  - Direct binding to FK506 binding protein/FKBP-12
  - Blocks mTORC1 activity
  - At high dose/long exposure, also blocks mTORC2
    - Likely because pulling mTOR out of the system.
    - Hard to gauge the degree of mTORC2 inhibition.

- **ATP-competitive mTOR kinase inhibitor**
  - Competitive binding to mTOR catalytic site
  - Blocks both mTORC1 and mTORC2
How does rapamycin block mTORC1?

- Rapamycin binds to the immunophilin FK506-binding protein 1A, FKBP12.
- FKBP12, when bound to rapamycin, binds mTOR.
- FKBP12/Rapamycin/mTOR/Raptor is inactive.

*Nature Reviews Immunology* 9, 324-337, 2009
Why wouldn’t these work well to reduce mTOR hyperactivation?

• Initially very exciting as potential anti-cancer drugs.
• HOWEVER:
• These pathways are VERY complicated.
• Crosstalk with other pathways is common.
Newer inhibitors are kinase inhibitors

David Sabatini: Torin
Inhibit both mTORC1 and mTORC2
Somewhat similar pathway complications as for rapalogs—although mTORC2 activation doesn’t occur

Nature Reviews Immunology 9, 324-337, 2009
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Sabatinilab.wi.mit.edu/researchDS.html