mTOR signaling and metabolic effects

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Increasing problem of obesity and diabetes among US adults

**Obesity**
(BMI ≥30 kg/m²)

<table>
<thead>
<tr>
<th>Year</th>
<th>US Adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>19.4</td>
</tr>
<tr>
<td>2005*</td>
<td>25.4</td>
</tr>
</tbody>
</table>

31% increase

**Diabetes**

<table>
<thead>
<tr>
<th>Year</th>
<th>US Adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>5.3</td>
</tr>
<tr>
<td>2005*</td>
<td>7.2</td>
</tr>
</tbody>
</table>

36% increase

*Jan–Sep

Numbers of persons with diabetes will more than double by 2030

US population with diabetes (millions)

- 2002: 13.9
- 2030: 30.3

118% increase

mTOR (mammalian target of Rapamycin)

- mTOR is a serine/threonine kinase P13K-related kinase
  - Regulation of cell growth
  - Glucose metabolism
  - Lipid metabolism
- Nucleates 2 distinct multi-protein complexes
  - mTORC1
    - Promotes cell growth
    - Prevents autophagy
    - ATP production
  - mTORC2
    - Regulates cell survival and cell metabolism
    - Cytoskeletal survival
mTORC1

- mTOR
- Raptor
- pras40
- deptor
- mLST8
- tti1-tel2

Amino acids

Energy levels

Stress

Growth factors (insulin and IGF1)

Rapamycin
Metformin

Autophagy

Protein and lipid synthesis
Cell cycle progression
Growth

mTORC2

- mTOR
- rictor
- mSin1
- protor1/2
- deptor
- mLST8
- tti1-tel2

Oxygen

Cell survival

Cytoskeleton organization

Metabolism

mTOR and effects on glucose metabolism

- mTOR and S6K1 mediate nutrient induced insulin resistance by down regulating Insulin receptor substrate proteins and thereby decreasing Akt phosphorylation.

- mTOR inhibitor [Rapamycin] worsened glycemia in P.Obesus DM+ mice, but no effect on P.Obesus DM- mice.

- P.Obesus DM+ mice have 10x serum insulin levels.
- Rapamycin completely abolished this increase.
- Rapamycin decreases muscle insulin sensitivity.
- Rapamycin decreases Bcell mass by 50% by ↑ apoptosis.
mTOR and effects on CHO metabolism

• Depends!
• depends on the level of mTORC1 activity
  - mTORC1 promotes insulin resistance in adipose tissue via S6K1 mediated inhibition of insulin signaling- IRS1
  - mTORC1 activity is increased in adipose tissue, skeletal muscle, liver of insulin resistant rodents
  - mTORC1 regulates β-cell mass (size and number) and function. Insulin secretion
  - S6K1-deficient mice have diminished β-cell mass, hypoinsulinemia and glucose intolerance
• Sustained activation of mTORC1 leads to β-cell exhaustion, apoptosis and glucose intolerance
Table 1: Incidence of hyperlipidemia and hyperglycemia induced by mTOR inhibitors in phase III studies.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Types of cancer</th>
<th>n</th>
<th>Hyperglycemia (%)</th>
<th>Hypercholesterolemia (%)</th>
<th>Hypertriglyceridemia (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>Grades 3-4</td>
<td>All grades 3-4</td>
<td>All grades 3-4</td>
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<tr>
<td>Everolimus</td>
<td>Renal cell carcinoma</td>
<td>269</td>
<td>50</td>
<td>12</td>
<td>76</td>
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<tr>
<td>Placebo (3)</td>
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<td>135</td>
<td>23</td>
<td>1</td>
<td>32</td>
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<tr>
<td>Everolimus</td>
<td>Pancreatic NETs</td>
<td>204</td>
<td>13</td>
<td>5</td>
<td>ND</td>
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<tr>
<td>Placebo (2)</td>
<td></td>
<td>203</td>
<td>4</td>
<td>2</td>
<td>ND</td>
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<tr>
<td>Everolimus + Oct</td>
<td>Gastrointestinal NETs</td>
<td>215</td>
<td>12</td>
<td>5</td>
<td>6</td>
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<td>Placebo + Oct (64)</td>
<td>Breast</td>
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<td>0.5</td>
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<tr>
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<td>482</td>
<td>13</td>
<td>4</td>
<td>ND</td>
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<tr>
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<td>238</td>
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<td>&lt;1</td>
<td>ND</td>
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<tr>
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<td>Subendymal giant cell astrocytoma with TBS</td>
<td>78</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
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<td>39</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Temsirolimus</td>
<td>Renal cell carcinoma</td>
<td>208</td>
<td>26</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Interferon</td>
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<td>200</td>
<td>11</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Temsi + Interferon (6)</td>
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<td>208</td>
<td>17</td>
<td>6</td>
<td>26</td>
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<tr>
<td>Temsirolimus + letrozole</td>
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<td>550</td>
<td>13</td>
<td>4</td>
<td>12</td>
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<tr>
<td>Placebo + letrozole (53)</td>
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<td>553</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Temsirolimus</td>
<td>Mantle cell lymphoma</td>
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<td>ND</td>
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<td>ND</td>
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<td>Investigator’s choice (7)</td>
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<td>53</td>
<td>ND</td>
<td>ND</td>
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</table>

NETs, neuroendocrine tumors; ND, not described (incidence are <10%); Oct, octreotide; TBS, tuberous sclerosis complex. Common terminology criteria for adverse events (CTCAE) grades for hyperglycemia: Grade 1, fasting blood glucose between 126 and 160 mg/dl (7.0–8.9 mmol/l); Grade 2, fasting blood glucose between 161 and 250 mg/dl (8.9–13.9 mmol/l); Grade 3, blood glucose between 251 and 500 mg/dl (13.9–27.8 mmol/l); Grade 4, blood glucose >500 mg/dl (27.8 mmol/l). CTCAE grades for hypercholesterolemia: Grade 1, total cholesterol between the upper limit of the normal range and 300 mg/dl (7.75 mmol/l); Grade 2, total cholesterol between 301 and 400 mg/dl (7.76–10.34 mmol/l); Grade 3, total cholesterol between 401 and 500 mg/dl (10.35–12.92 mmol/l); Grade 4, total cholesterol >500 mg/dl (12.92 mmol/l). CTCAE grades for hypertriglyceridemia: Grade 1, triglycerides between 150 and 300 mg/dl (1.71–3.42 mmol/l); Grade 2, triglycerides between 301 and 500 mg/dl (3.43–5.70 mmol/l); Grade 3, triglycerides between 501 and 1000 mg/dl (5.71–11.4 mmol/l); Grade 4, triglycerides >1000 mg/dl (11.4 mmol/l).
mTOR inhibitors and Glucose metabolism

• Sirolimus (Rapamycin)
• Everolimus
• Temsilorimus

• Sirolimus
  - In renal transplant pts. 21.9% cumulative incidence of NOD, when used with calcineurin inhibitors

• Everolimus/Temsilorimus
  - Hyperglycemic effect is less pronounced
  - Different patient population - Chemotherapy
Relationship between mTORC1 activity and metabolic homeostasis.