Wnt signaling

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Wnt Signaling

- **Wnt** consists of a family of secretory glycoproteins (19 genes) with MW ~40Kd

- Wnt signaling was initially known for its roles in regulation of embryonic development and association with tumorigenesis.

- Wnt signaling has now been shown to be involved in a wide range of biological and pathophysiological processes, including neuronogenesis, organogenesis, adipogenesis, myogenesis, bone development, lipid and glucose metabolism, and stem cell biology.
Wnt signaling regulates neuronal migration and positioning

Wnt signaling controls Q cell and HSN migration along the A-P axis in *C. elegans*

Wnts regulate the terminal arborization of axons and dendritic morphogenesis.

Wnts regulate the assembly of synapses

Mouse cerebellar cortex

Canonical Wnt signaling

- **Wnt**
- **Fz1-10**
- **LRP5/6**
- **APC**
- **Axin**
- **Dvl**
- **β-catenin**

Gene transcription
Wnt signaling pathways

Canonical Pathway
- APC
- Wnt
- LRP
- β-catenin
- TCF/LEF
- Transcription regulation

Non-canonical Pathway
- JNK
- PKC
- Ca^{2+}

Wnt1, 2, 3, 3a, 7a, 7b, 8

Wnt4, 5a, 5b, 6, 10a, 11
Wnt coreceptor LRP5/6

Axin interaction

Effect of phosphatidylinositol lipid kinase siRNAs on the levels of pSer^{1490} of LRP6

Phosphatidylinositol 4-kinase type IIα

Phosphatidylinositol 4-phosphate 5-kinase type Iβ

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Phosphatidylinositol lipid metabolism

\[
\text{PI4KII} \quad \rightarrow \quad \text{PIP5KI} \\
\text{PtdIns} \quad \rightarrow \quad \text{PtdIns(4)P} \quad \rightarrow \quad \text{PtdIns (4,5)P}_2 \quad \rightarrow \quad \text{IP3+DAG} \rightarrow \quad \text{PtdIns (3,4,5)P}_3
\]

- Cytoskeletal reorganization
- Channel activity
- Endocytosis
- Vesicle transport
- etc....

PLC

PI3K
Effect of PI kinase siRNAs can be rescued by direct delivery of PIs

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Reduction in PIP\(_2\) levels leads to decrease in LRP6 phosphorylation


![Diagram showing reduction in PIP\(_2\) levels and decrease in LRP6 phosphorylation](image)

<table>
<thead>
<tr>
<th>Condition</th>
<th>p-S1490-</th>
<th>LRP6-</th>
<th>Wnt3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mock</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>FRP+FKBP</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FRP+FKBP-INPP</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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Wnt3a stimulates PIP$_2$ production

The Lipid Core

Dionex HPLC with the conductivity detector

Wnt3a treatment 0, 15, 30 mins

PIP$_2$ levels (fold)

0  15  30
0  1  2  3

* P<0.05 vs. Time 0

Louise Lucast, Weijun Pan
Wnt3a-stimulated PIP$_2$ production depends on PIP5KI

HEK293T

siRNA: Ctr 5K1β

PtdIns(4,5)P$_2$ (fold)

- Wnt3a + Wnt3a

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Wnt3a-stimulated PtdIns (4,5)P$_2$ production depends on Fz, but not LRP5/6

* P<0.05 vs. -Wnt3a

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Wnt3a-stimulated PIP$_2$ production depends on Dvl

* P<0.05 vs. -Wnt3a

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Dvl directly interacts with and stimulates PIP5KI
A model for Wnt cross-membrane signaling
Future direction 1: Regulation of PI4P formation by Wnt

Laura Swan
Future direction 2: Phosphoproteomes of Wnt-treated cells
Wnt Signaling

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