SBGN Activity Flow Diagram

Huaiyu Mi
For the SBGN Team
http://sbgn.svn.sourceforge.net/viewvc/sbgn/ActivityFlow/
**A Mutant-p53/Smad Complex Opposes p63 to Empower TGFβ-Induced Metastasis**

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**Twist-1 Is a PPARδ-Inducible, Negative-Feedback Regulator of PGC-1α in Brown Fat Metabolism**

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**SUMMARY**

Brown fat is specialized for energy expenditure, a process that is principally controlled by the transcriptional coactivator PGC-1α. Here, we describe a molecular network important for PGC-1α function and brown fat metabolism. We find that twist-1 is selectively expressed in adipose tissue, interacts with PGC-1α, and is recruited to the promoters of PGC-1α’s target genes to suppress mitochondrial metabolism and uncoupling. In vivo, transgenic mice expressing twist-1 in the adipose tissue are prone to high-fat-diet-induced obesity, whereas human brown fat cells are of physiological and pharmacological significance. On the other hand, it has long been observed that brown fat cells in humans have a remarkable capacity for brown fat thermogenesis. It is highly influenced by nutritional and environmental cues. Both overexpression and loss-of-function studies demonstrate that PGC-1α regulates the entire program of thermogenesis.

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Activity Flow Diagram

Symbols

- Activity nodes
  - Auxiliary information
- Container nodes
- Modulation arcs
- Logic operators
Activity Node (AN)

-Biological activity

- Each node represents an activity, but not the entity.
- Multiple ANs can be used to represent activities from one entity, e.g., receptor protein kinase, and ligand gated ion channel.
- One AN can be used to represent activities from a group of entities (e.g., a complex).
Activity Nodes

- LABEL
- Perturbation
- LABEL
- Observable
Unit of Information

A

LABEL

B

LABEL

C

LABEL

D

LABEL

E

LABEL
Unit of Information
-Examples

A
- MAPK activity

B
- MAPK activity

C
- cAMP activity

D
- kinase activity

E
- SNARE activity
Container
-Compartment

![Diagram of Container with e:INFO and LABEL]
Modulation Arcs

- **Positive influence**
- **Negative influence**
- **Unknown influence**
- **Trigger**
Logic Operators

- AND
- OR
- NOT
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SUMMARY

TGFβ ligands act as tumor suppressors in early stage tumors, driving inhibitory innate immune responses and pro-invasive factors in advanced cancers. The molecular nature of this switch remains enigmatic. One of the most frequent genetic lesions in human tumors is mutation of the p53 tumor suppressor, which acts as transcription factor to promote cytostasis, apoptosis and genome integrity. In addition, recent evidence points to a role of TGFβ signaling in promoting metastasis. Here, we show that these converge on the same mechanism: Ras-activated mutant-p53 and TGFβ/Smad signaling plays a central role for tumorigenesis of several epithelia, paradoxically switching from tumor suppressor to promote growth and survival, also prefigure undefined properties that render mutant-p53 a dominant prometastatic factor. Whether this entails the intersection with other prometastatic switches of mutant-p53 and TGFβ lies in the question of whether the generation of mutant-p53 knockin mice (Caulin et al., 2007; Hingorani et al., 2005). Remarkably, tumors emerging in these models appear critical for the malignant phenotypes of mutant-p53 tumors but are paradoxically diverted into potent metastatic factor. Whether this entails the intersection with other prometastatic switches of mutant-p53 and TGFβ lies in the question of whether the generation of mutant-p53 knockin mice (Caulin et al., 2007; Hingorani et al., 2005). Remarkably, tumors emerging in these models appear critical for the malignant phenotypes of mutant-p53 tumors but are paradoxically diverted into potent metastatic factor.
Twist-1 Is a PPARδ-Inducible, Negative-Feedback Regulator of PGC-1α in Brown Fat Metabolism

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SUMMARY

Brown fat is specialized for energy expenditure, a process that is principally controlled by the transcriptional coactivator PGC-1α. Here, we describe a molecular network important for PGC-1α function and brown fat metabolism. We find that twist-1 is selectively expressed in adipose tissue, interacts with PGC-1α, and is recruited to the promoters of PGC-1α's target genes to suppress mitochondrial metabolism and uncoupling. In vivo, transgenic twist-1 expression reveals an unexpected physiological role for twist-1 in the main-regulatory mechanism. These findings reveal a molecular network important for PGC-1α function and brown fat metabolism, including a negative-feedback mechanism that regulates the actions of PGC-1α.

In the form of triglycerides and released them in times of energy need. By contrast, brown fat is specialized for energy expenditure by dissipating energy as heat, a process termed as adaptive thermogenesis (Cannon and Nedergaard, 2004; Lowell and Spiegelman, 2005). The unique metabolic property of brown fat is due to its high mitochondrial density and fuel oxidation capacity, and to its exclusive expression of uncoupling protein-1 (UCP1) in the inner mitochondrial membrane, which uncouples the mitochondrial proton gradient from ATP production. Given the fundamental importance of adipose tissues in the maintenance of systematic energy homeostasis, their functions must be tightly regulated.

As a heat-generating organ, brown fat plays a key part in the regulation of energy balance and obesity, as evidenced in rodent studies. For instance, either ablation of brown fat through expression of a toxic transgene or knock-out of UCP1 leads to high susceptibility to diet-induced obesity (Kontani et al., 2005; Lowell et al., 1993), whereas increase of UCP1 expression protects animals against diet-induced obesity (Kopecky et al., 2007; Lowell et al., 1993).

However, recent studies reveal that white fat cells, which normally do not possess discrete brown fat depots, and brown fat cells are dispersed within white fat, casting doubt on whether a long-term imbalance between energy intake and energy expenditure. Adipose tissues serve as major sites for the control of energy balance. They are present in two functionally distinct types: white fat and brown fat. White fat stores excess energy in the form of triglycerides and releases them in times of need. By contrast, brown fat is specialized for energy expenditure by dissipating energy as heat, a process termed as adaptive thermogenesis (Cannon and Nedergaard, 2004; Lowell and Spiegelman, 2005). The unique metabolic property of brown fat is due to its high mitochondrial density and fuel oxidation capacity, and to its exclusive expression of uncoupling protein-1 (UCP1) in the inner mitochondrial membrane, which uncouples the mitochondrial proton gradient from ATP production. Given the fundamental importance of adipose tissues in the maintenance of systematic energy homeostasis, their functions must be tightly regulated.

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Activity Flow Diagram Example
-sodium channel activation

increase in membrane potential

sodium channel activity

increase in membrane potential

sodium channel gating activity

sodium channel conductance activity

depolarization

depolarization

IN

-V

NH₃⁺

α

β₂

β₁

+H₃N

OUT

CO₂⁻

Voltage Sensing

Inactivation

Modulation

P

P

P

P

P
Activity Flow Diagram Example
- EGF Receptor

EGF activity

EGFR binding

EGFR kinase activity

RAS activity

EGF activity

EGFR binding

EGFR kinase activity

RAS activity
• AF diagrams are ambiguous.

• An AF diagram should be associated with either a PD or ER diagram, if possible.
• Issues?

• Discuss and resolve remaining issues at this meeting (time and location TBD)

• Finish the draft and circulate for feedback by ??