SBGN Activity Flow Diagram

Huaiyu Mi
For the SBGN Team

http://sbgn.svn.sourceforge.net/viewvc/sbgn/ActivityFlow/

From Cell 137, April 3, 2009

A Mutant-p53/Smad Complex Opposes p63 to Empower TGFβ-Induced Metastasis

Maddalena Adorno,[1,8] Michelangelo Cordenonsi,[1,8] Marco Montagner,[1] Sirio Dupont,[1] Christine Wong,[2] Byron Hann,[2] Aldo Solari,[3] Sara Bobisse,[4] Maria Beatrice Rondina,[4] Vincenza Guzzardo,[5] Anna R. Parenti,[5] Antonio Rosato,[4,6] Silvio Bicciato,[6,7] Allan Balmain,[2] and Stefano Piccolo[1,*]

[1]Department of Histology, Microbiology and Medical Biotechnologies, University of Padua School of Medicine, viale Colombo 3, 35100 Padua, Italy
[2]Cancer Research Institute, University of California, San Francisco, 2340 Sutter Street, San Francisco, CA 94115, USA
[3]Department of Chemical Engineering Processes, University of Padua, via F. Marzolo 9, 35131, Padua, Italy
[4]Department of Oncology and Surgical Sciences and Istituto Oncologico Veneto, University of Padua, via Gattamelata 64, 35126 Padua, Italy
[5]Department of Medical Diagnostic Science and Special Therapies, Section of Pathology, University of Padua, viale Gabelli 2, 35126 Padua, Italy
[6]Istituto Oncologico Veneto, via Gattamelata 64, 35126 Padua, Italy
[7]Department of Biomedical Sciences, University of Modena and Reggio Emilia, via G. Campi 287, 41100, Modena, Italy
[8]These authors contributed equally to the work
*Correspondence: piccolo@civ.bio.unipd.it
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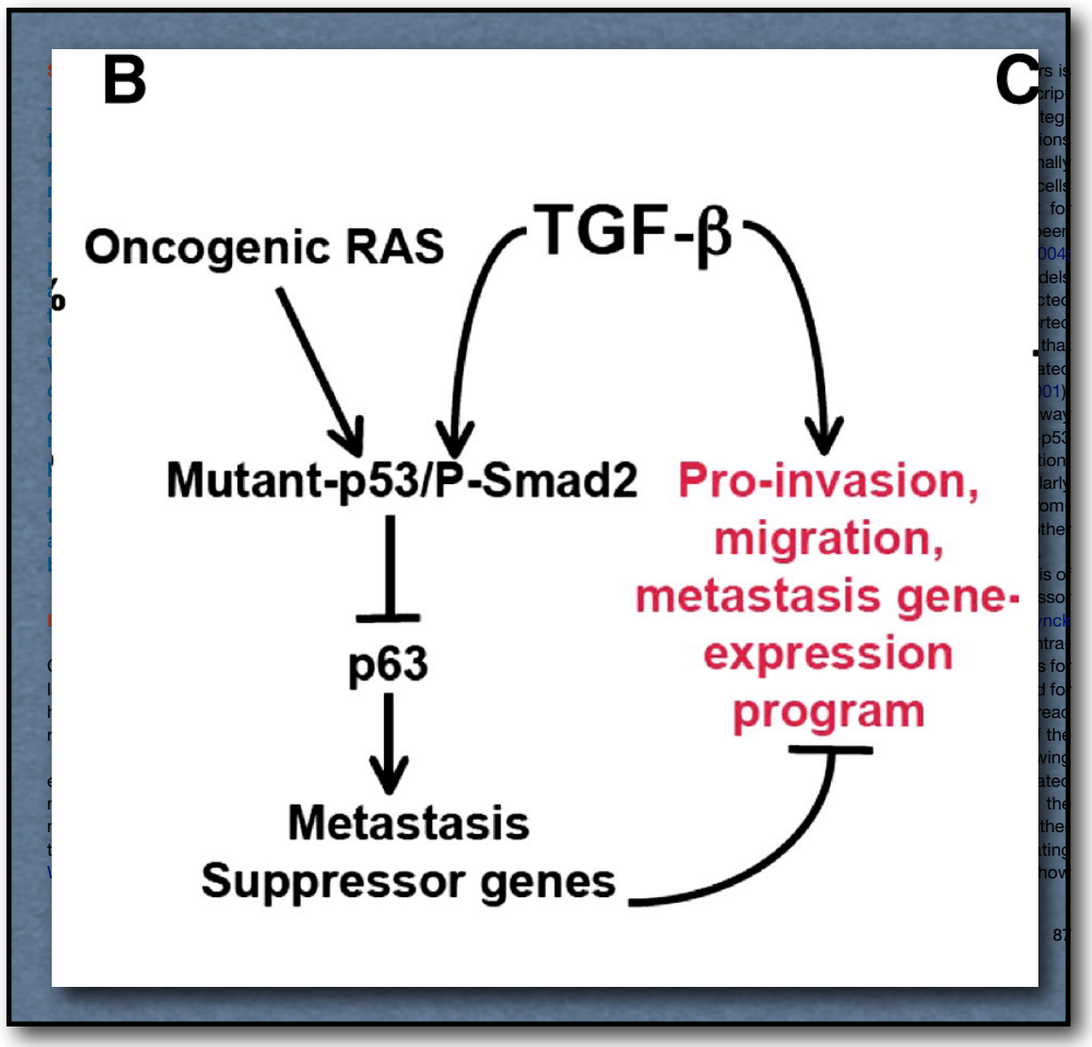

Twist-1 Is a PPARδ-Inducible, Negative-Feedback Regulator of PGC-1α in Brown Fat Metabolism

Dongning Pan,[1,2] Masaki Fujimoto,[1,2] Andrea Lopes,[1] and Yong-Xu Wang[1,*]

[1]Program in Gene Function and Expression and Program in Molecular Medicine, University of Massachusetts Medical School, 364 Plantation Street, Worcester, MA 01605, USA
[2]These authors contributed equally to this work
*Correspondence: yongxu.wang@umassmed.edu
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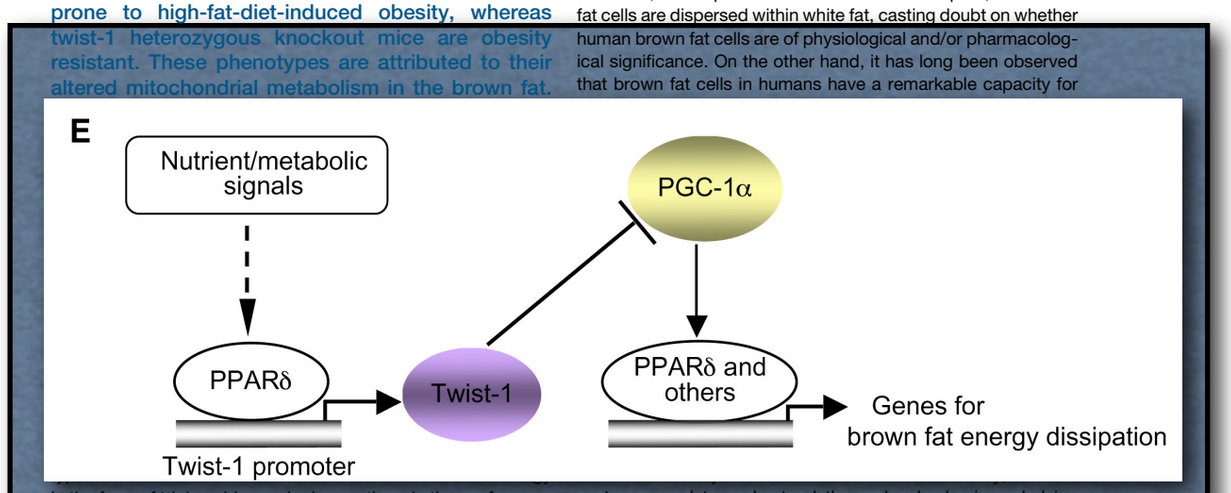
SUMMARY

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 twist-1 heterozygous knockout mice are obesity resistant. These phenotypes are attributed to their altered mitochondrial metabolism in the brown fat.



in the form of triglycerides and releases 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, 2000). 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.

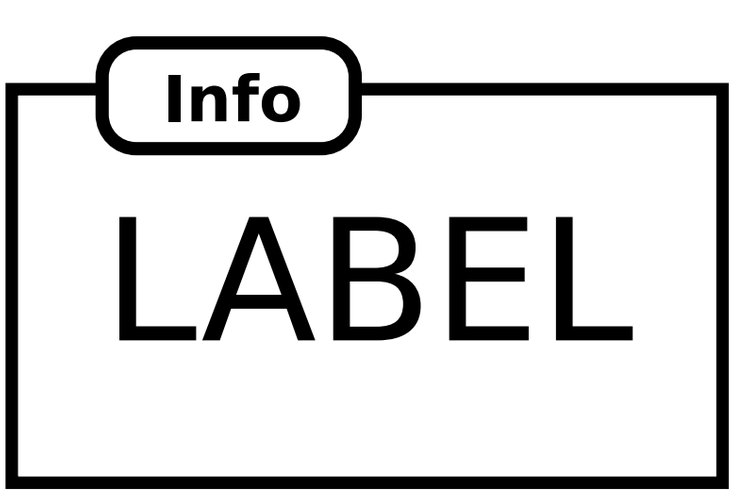
As a heat-generating organ, brown fat plays a key part in the regulation of energy balance and obesity, as evidenced in rodent studies. For instance, either ablation of brown fat through expression of a toxic transgene or knockout of UCP1 leads to high susceptibility to diet-induced obesity (Kontani et al., 2005; Lowell et al., 1993), whereas increase of UCP1 expression protects animals against diet-induced obesity (Kopecky et al., 1995). However, human adults, unlike rodents and human neonates, do not possess discrete brown fat depots, and brown fat cells are dispersed within white fat, casting doubt on whether human brown fat cells are of physiological and/or pharmacological significance. On the other hand, it has long been observed that brown fat cells in humans have a remarkable capacity for a strong need to understand the molecular basis underlying brown fat metabolism.

A central regulator in brown fat thermogenesis is the transcriptional coactivator PGC-1α (reviewed in Lin et al., 2005). PGC-1α is predominantly expressed in the brown fat, and its expression 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

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

Perturbation

Observable

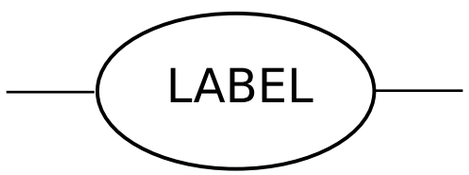
Unit of Information

A

B

C

D

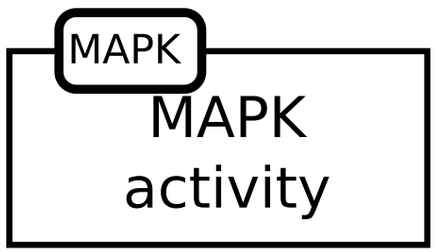


E

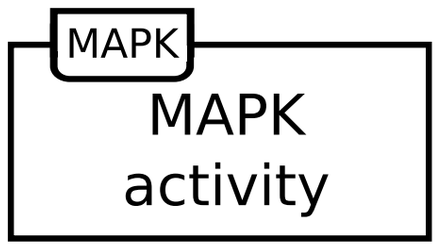
Unit of Information

-Examples

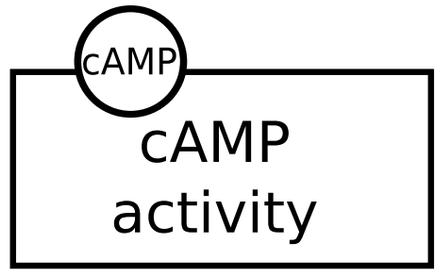
A



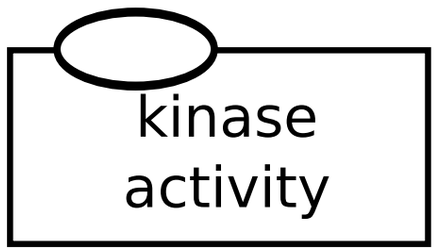
B



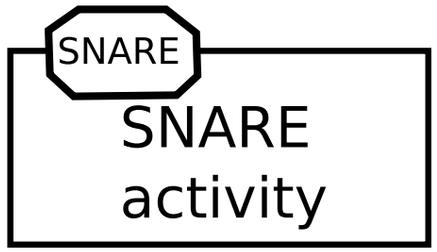
C



D

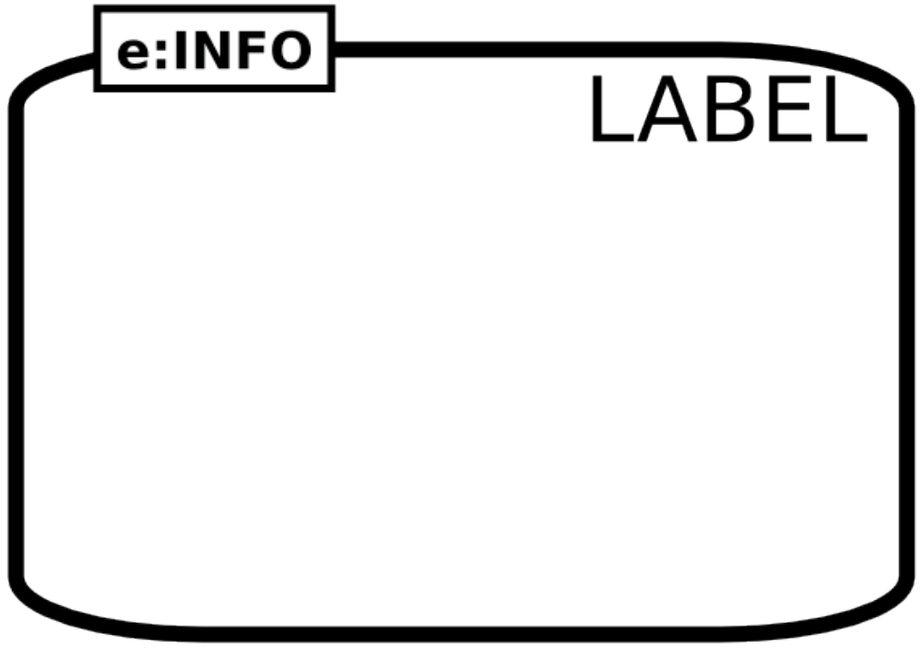


E



Container

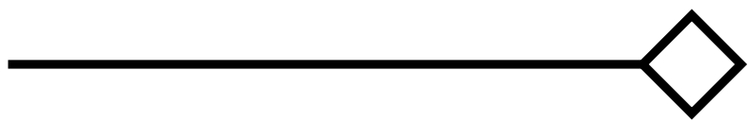
-Compartment



Modulation Arcs

Positive influence

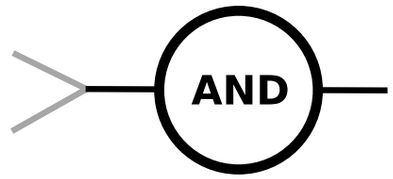
Negative influence

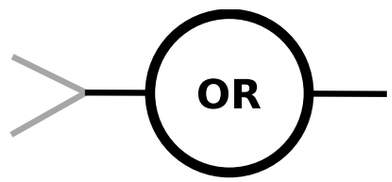


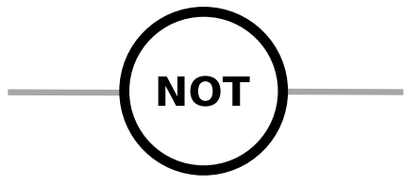
Unknown influence

Trigger

Logic Operators







Cell

From Cell 137, p. 87-p. 98, April 3, 2009

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[8]These authors contributed equally to the work
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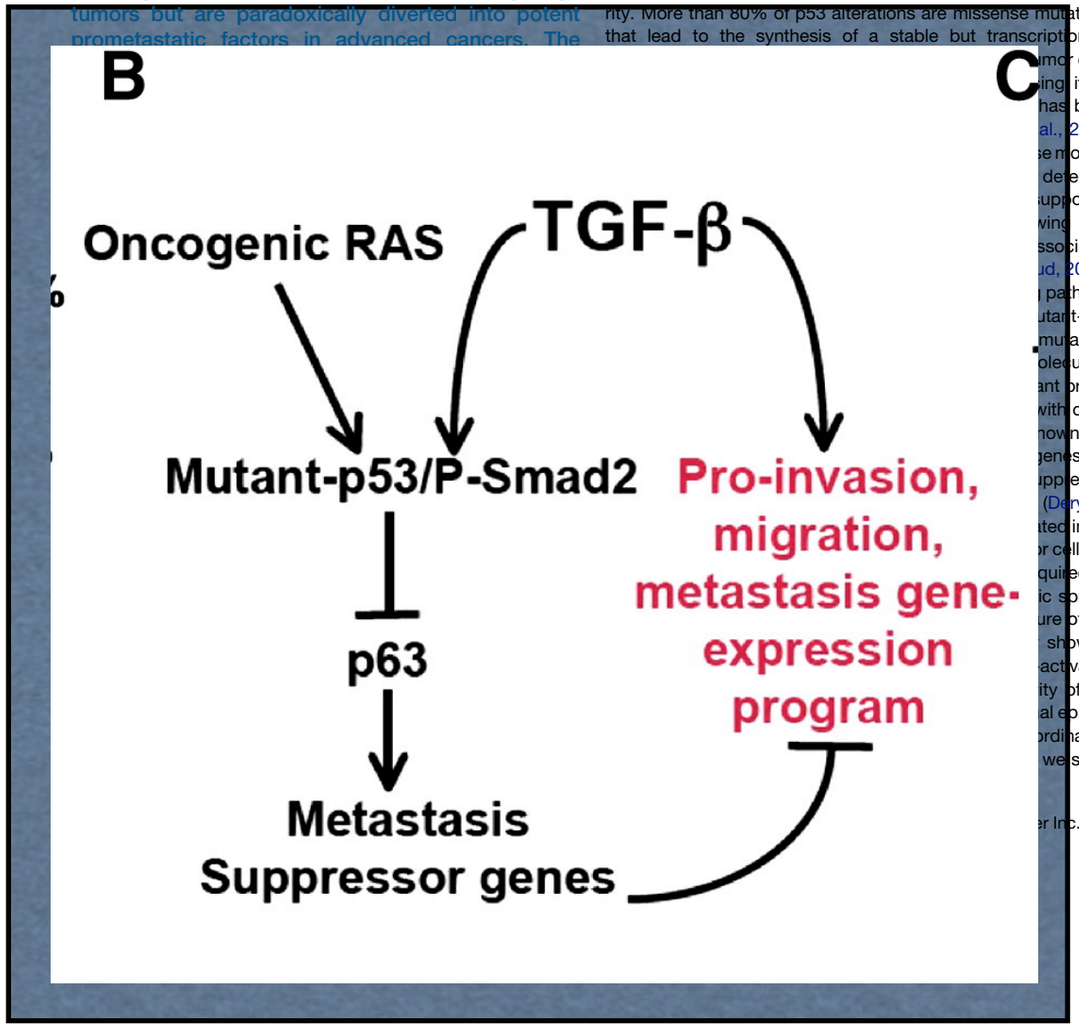
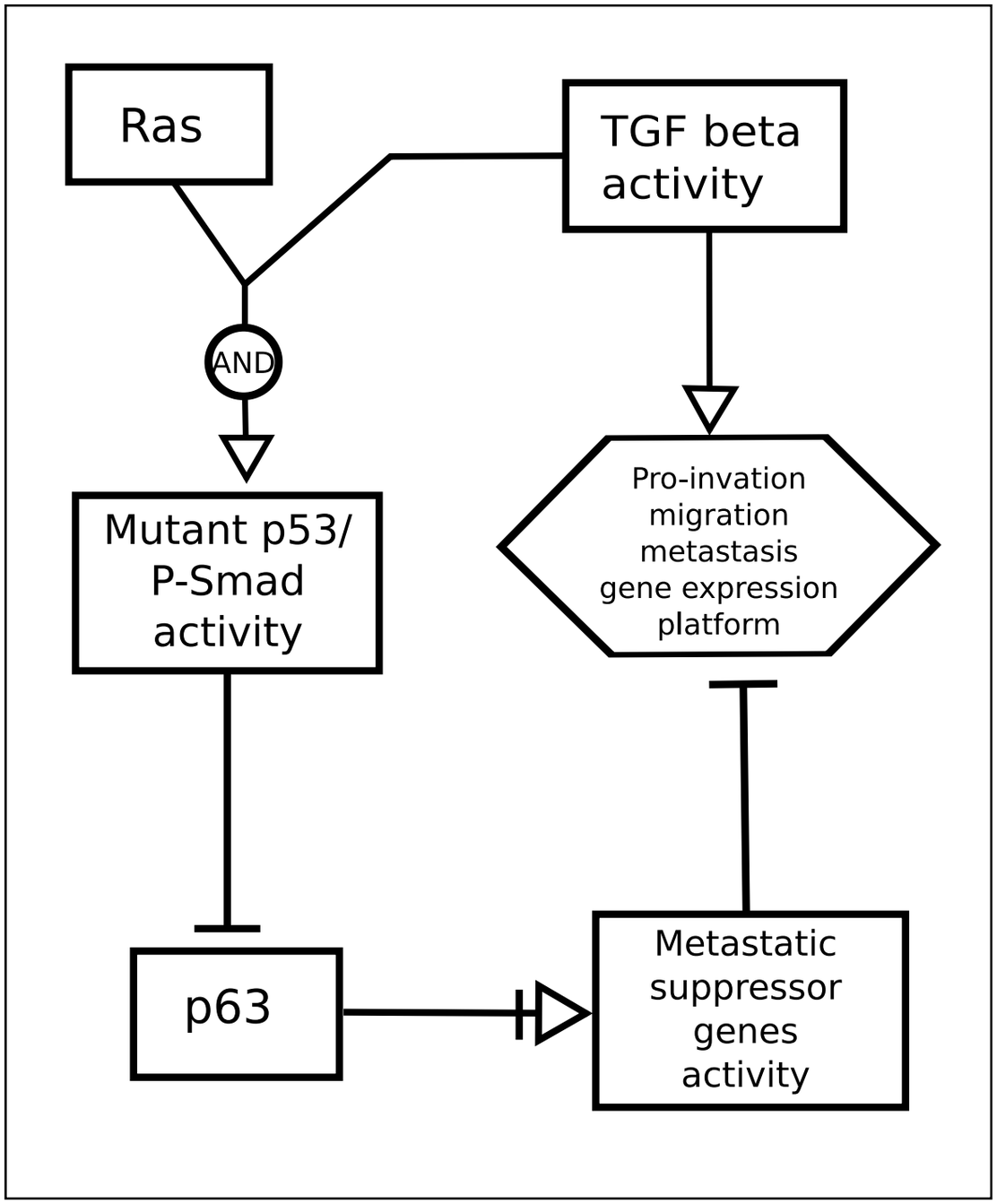
SUMMARY

TGFβ ligands act as tumor suppressors in early stage tumors but are paradoxically diverted into potent prometastatic factors in advanced cancers. The



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. More than 80% of p53 alterations are missense mutations that lead to the synthesis of a stable but transcriptionally



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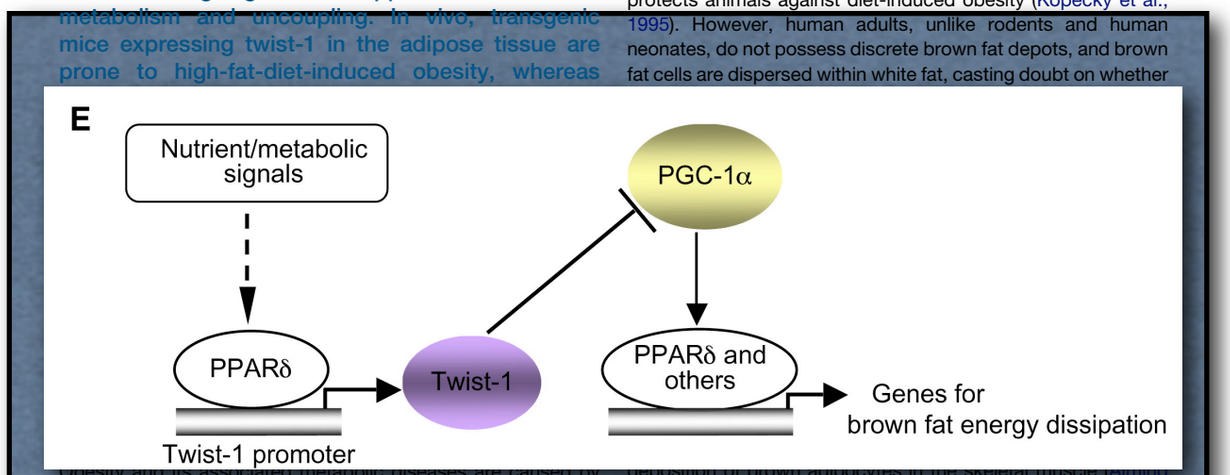

Obesity and its associated metabolic diseases are caused by a long-term imbalance between energy intake and energy expenditure. Adipose tissues serve as major sites for the control of energy balance. They are present in two functionally distinct types: white fat and brown fat. White fat stores excess energy in the form of triglycerides and releases them in times of 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, 2000). 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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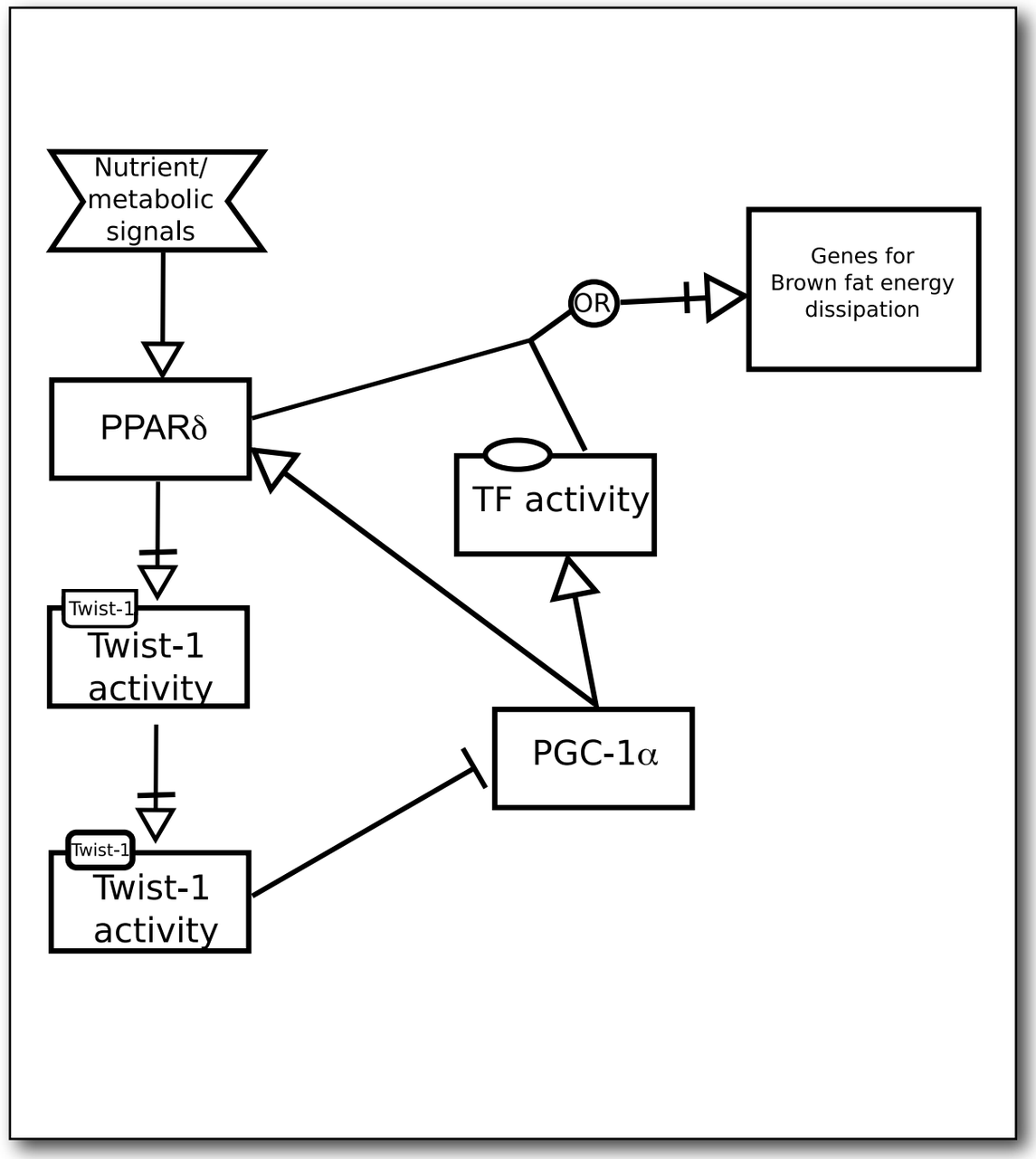
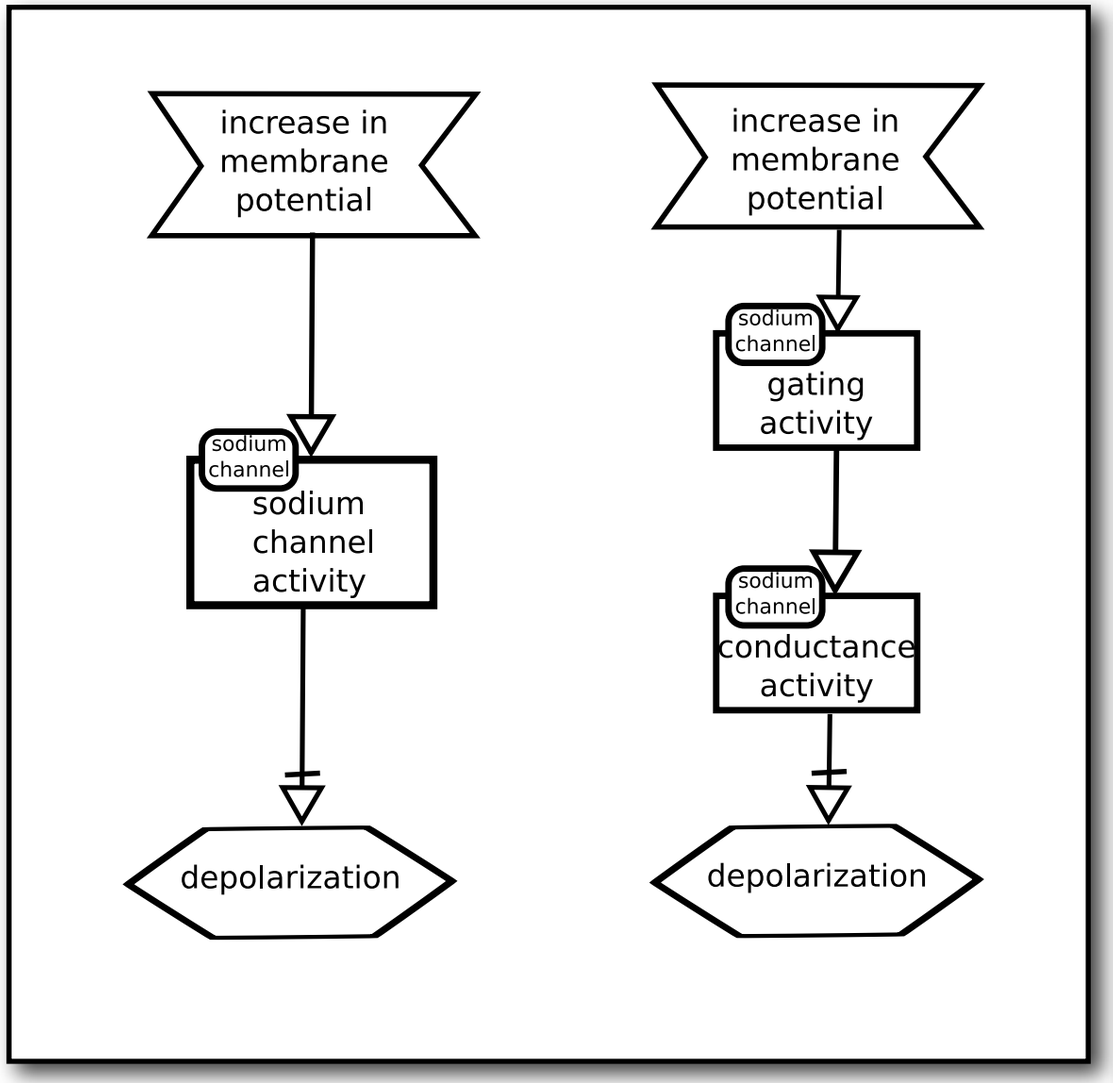
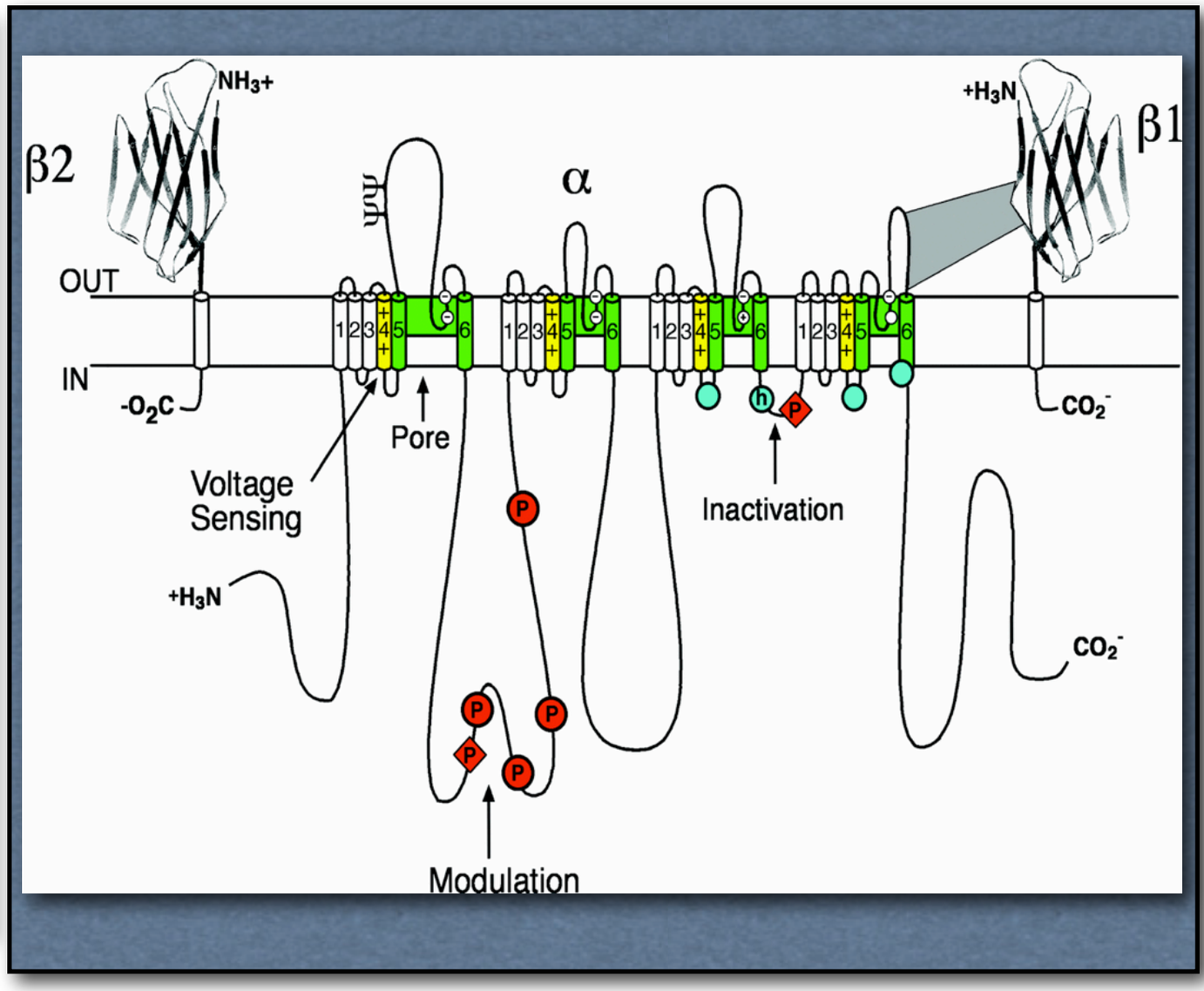
A central regulator in brown fat thermogenesis is the transcriptional coactivator PGC-1α (reviewed in Lin et al., 2005). PGC-1α is predominantly expressed in the brown fat, and its expression is highly influenced by nutritional and environmental cues. Both overexpression and loss-of-function studies demonstrate that PGC-1α regulates the entire program of thermogenesis



Activity Flow Diagram Example

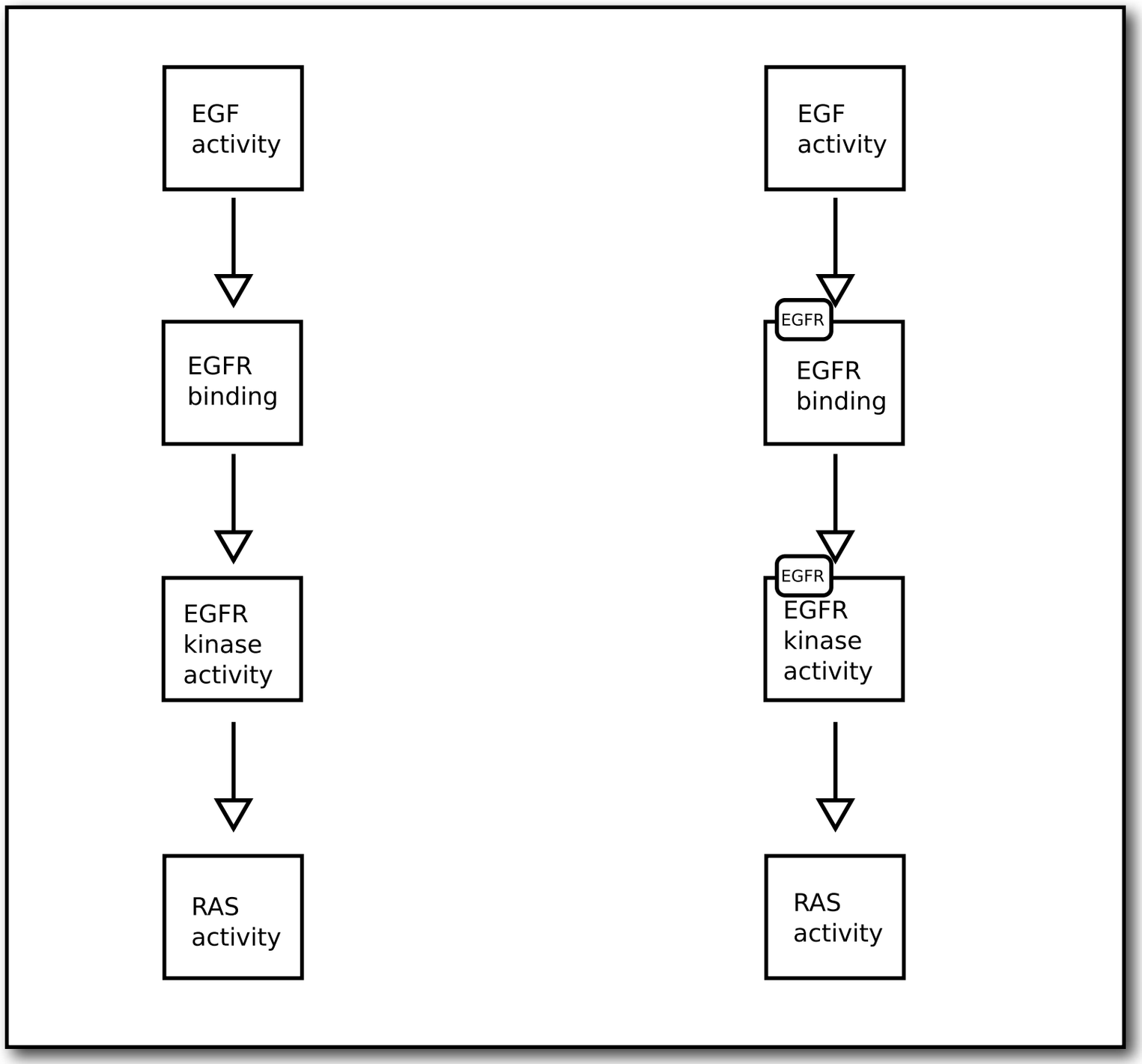
-sodium channel activation





Activity Flow Diagram Example

- EGF Receptor



- 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 ??