Understanding how signaling networks evolve

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Signaling networks: connecting cells with the outside world
Signaling networks: connecting cells with the outside world

Images: http://www.fi.edu
Signaling networks: connecting cells with the outside world
Signaling networks: connecting cells with the outside world

Signal A  Signal B  Signal C

Signal Processing & Integration

Outputs
Signaling networks are made of multiple proteins and genes

Image: wikipedia
Lab Interests: Signaling Networks

- Evolution
- Disease
- Engineering
How does this complexity evolve?
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How does this complexity evolve?
Modularity in Transcriptional Circuits Is Believed to Play an Important Role in Evolution

Transcriptional Nodes

INPUT

cis-element

OUTPUT

gene

new function

recombination of cis-elements and genes

David Kingsley & colleagues

Sean Carroll & colleagues
Modularity in Transcriptional Circuits Is Believed to Play an Important Role in Evolution

However, evolution mediated by shuffling of genetic elements controlling gene expression is limited to processes that do not need fast responses.
How do processes that require faster responses evolve?
How do processes that require faster responses evolve?
Proteins are organized in distinct domains with modular functions.
Modularity in protein function regulation could play an important role in the evolution of fast cellular processes.

Re-wiring of transcriptional nodes leads to changes in slow responses.

Re-wiring of signaling nodes leads to changes in fast responses.
Modular allosteric regulation controls signaling protein functions

Regulatory domain
- Bind activated Cdc42

Modular protein
- WHD
- GBD
- EVH1
- SH3
- SH2
- Voltage sensor

Catalytic domain
- WHD
- B
- pro-rich
- VCA
- EVH1
- B
- GBD
- pro-rich
- VCA
- GBD
- IS
- Kinase
- SH3
- SH2
- Kinase
- SH2
- Phosphatase
- Voltage sensor
- Pore
- Cl-VSP

Activation of actin polymerization
Protein phosphorylation
Phosphoinositide dephosphorylation
One of our research goals:

Exploring the role of protein domain shuffling in the evolution of signaling networks
The Yeast Mating Pathway

alpha-factor

MAPKKK
MAPKK
MAPK
Downstream Effects
Synthetic Biology/Laboratory Evolution Approach
Quantitative Analysis of Large Collections of Strains
Quantitative Analysis of Large Collections of Strains
Domain Recombination Leads to Rapid Diversification of Mating Pathway Response Dynamics
Does Domain Recombination Affect Mating Efficiency as Well?

WT or library \{ a, \alpha \} \rightarrow a/\alpha
Domain Recombination Leads to Strains that Mate More Efficiently than Wild Type

WT or library → a/α

Circle Area = Mating Efficiency (relative to WT)
Why are there variants that mate better than WT (in the lab)?
Why are there variants that mate better than WT (in the lab)?
Understanding the Mechanisms that Result in Response Changes
Fluorescence Microscopy Experiments Suggest Possible Mechanisms Leading to Changes in Response Dynamics
Understanding the Mechanisms that Result in Response Changes
Understanding the Mechanisms that Result in Response Changes

Mating Pheromone

Ste2 Gpa1 Ste4 Ste18 Cdc42

Ste5 Ste7 Fus3

Ste11 Ste20 Ste50
Understanding the Mechanisms that Result in Response Changes
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[Diagram of mating pheromone response pathway]

- Ste2
- Gpal
- Ste5 [N]-Ste11 [C]

[GFP fluorescence over time graph]

- Ste5
- Fus3
- Ste7
- Ste11
- Ste20
- Cdc42
- Ste4
- Ste18

[Graph showing time in minutes and GFP fluorescence in AU]
Understanding the Mechanisms that Result in Response Changes
Would domain recombination still lead to adaptive evolutionary change when at least one wild type gene is deleted?
Would domain recombination still lead to adaptive evolutionary change when at least one wild type gene is deleted?
Network re-wiring in the absence of the Ste11 kinase
Network re-wiring in the absence of the Ste5 scaffold

- Pathway activation (GFP)
- + pheromone
- - pheromone
Network re-wiring in the absence of the Ste20 kinase

Pathway activation (GFP)

+ pheromone
- pheromone
Network re-wiring in the absence of the Ste7 kinase
Conclusions

• Recombination of modular protein domains leads to the rapid diversification of signaling pathways.

• While domain duplication could lead to dominant negative effects, recombination is needed to create novel pathway responses.

• Most significant changes result from recombination events that alter the localization and/or regulation of catalytic domains.

• Mating network is very plastic, tolerating recombination events that involve deletions of WT genes.
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