Mechanistic dissection of Drosophila apoptotic switch

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***Short Abstract* — The molecular switch mechanism of apoptosis in *Drosophila* is studied for the first time by mathematical modeling. Enumeration of the elementary reactions in the model demonstrates that the molecular interactions among the signaling components are considerably different from their mammalian counterparts, despite the conserved apoptosis pathway. The model is calibrated by an experimental input-output relationship and the simulated trajectories exhibit all-or-none behavior. Bifurcation diagrams confirm that the model of *Drosophila* apoptotic switch possesses bistability. The bistable activation of the effector caspase to the apoptosome scaffolding protein is reversible, rather than irreversible as in mammals. Further analysis shows that the key to the systems property of reversibility lies in the double-negative feedback from the effector caspase to the initiator caspase.**

***Keywords* — Drosophila, apoptosis, molecular switch, mathematical model, bistability, double-negative regulation**

I. Introduction

APOPTOSIS is an evolutionarily-conserved process of autonomous cell death [1]. In contrast to the intense theoretical modeling work on mammalian apoptosis pathways, the apoptotic signaling mechanisms in the fruit fly, *Drosophila*, have not been investigated theoretically, to our best knowledge. Previous theoretical studies from the viewpoint of systems theory suggest that the mechanistic property of bistability can achieve the switch-like behavior of apoptosis. Consensus exists that the models of apoptosis networks are necessarily bistable, with one discrete stable steady state (inactive effector caspase) corresponding to cell survival, and the other (active effector caspase) to cell death [2, 3]. We ask, for the conserved function of apoptosis, whether the cellular regulatory system in *Drosophila* behaves the same as that in mammals or not.

II. Results

A. Modeling of the Drosophila apoptosis pathway

We first identify the essential signaling components from literature, which all have mammalian homologs. However, although the schematic regulations along the *Drosophila* pathway resemble their mammalian counterparts, the underlying molecular reactions have substantial degree of distinction. The most-upstream signaling proteins are upregulated by extrinsic stimuli, making the model an *intrinsic-extrinsic* hybrid type [4]. Moreover, the regulations of the initiator caspase DRONC is complicated, due to the combinatorial cleavage of two functional protein domains. A notable distinction in the network organization is the double-negative feedback from the effector caspase to the initiator caspase, while mammals have a direct positive feedback [5]. The calibrated model presents all-or-none time trajectories.

B. Reversible bistability and feedback topologies

Bifurcation diagrams of the steady state of the effector caspase versus varying single parameters or pairs of parameters show that the model of *Drosophila* apoptosis pathway is bistable in an extended region surrounding the nominal parameter set.

The bifurcation diagram of the response of effector caspase versus DARK input, the homolog of mammalian APAF1, shows that this essential bistable response is reversible. Further analysis of the *Drosophila* models containing different combinations of topologies, either with only the double-negative feedback, or with only the direct positive feedback, or with both feedback loops, demonstrate that the distinct double-negative feedback is the mechanism responsible for the reversible bistability in *Drosophila*.

III. Conclusion

The model of the *Drosophila* apoptosis pathway presents robust bistability. However, in contrast to the irreversible bistability of the caspase response to the APAF1 induction in mammals, the caspase activation elicited by DARK is reversibly bistable, which arises from the absence of the direct feedback activation of the initiator caspase by the effector caspase. Due to the essential role played by irreversibility in the robust apoptosis decision in mammals, our finding highlights an important mechanistic distinction between the apoptotic switch in flies and that in mammals. The results indicate plausible systems-level evolution of a conserved cellular function.

References

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