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Putting Rb in context with JNK

Comment on: Clavier A, et al. Two different specific JNK activators are required to trigger apoptosis or compensatory proliferation in response to Rbf1 in drosophila. Cell Cycle 2015; http://dx.doi.org/10.1080/15384101.2015.1100776.

Beth Stronach*; University of Pittsburgh School of Medicine; Department of Microbiology and Molecular Genetics; Pittsburgh, PA USA; *Correspondence to: Beth Stronach; Email: stronach@pitt.edu; http://dx.doi.org/10.1080/15384101.2015.1113786

A magnanimous sheriff was Rb. Called to high duty was he; to protect his commission from excessive division. Turned fugitive in cancer, sadly.

Infamous as a tumor suppressor, the Retinoblastoma protein, pRb, is inactivated in an astonishing number of human cancers, for which the evasion of growth control is a hallmark property.[1] Accordingly, a major function of Rb normally is to prevent the transcription of genes required for cell cycle progression. Envision Sheriff Rb stopping the E2F gang from ordering another round at the cell cycle saloon! But without Rb, the rowdy bandits celebrate entry into the S-phase, or DNA synthesis phase, of the cell cycle even if it's past curfew. Reactivating Rb might therefore be a desirable therapeutic intervention to inhibit cell cycle reentry. However, if cell division is required for normal development or tissue repair, increased Rb activity could lead to inappropriate cell cycle arrest, perhaps resulting in smaller organs or tissue loss. Given that the balance between cell division and cell death is critical for overall organism homeostasis, untangling the mechanisms by which Rb regulates this balance is particularly relevant in a clinical setting.[2]

One model system that has proven useful to specifically investigate the involvement of Rb in apoptosis is the developing *Drosophila* larva with its numerous proliferative epithelia in the form of imaginal discs, which grow, differentiate, and metamorphose into the visible adult appendages of the fly. In previous work, the Guenal lab observed that overexpression of Rbf (the fly Rb homolog) resulted in some loss of adult tissue, due to induction of apoptosis; however, cell death was limited to proliferating cells, whereas post-mitotic cells were unaffected.[3] The implication was that the proliferative status of the cells contributed to the contextual effects of Rb pro-apoptotic activity. In many organisms, the Jun kinase (JNK) pathway is triggered in cells that have suffered an insult and can drive apoptosis in a caspase-dependent manner. Suspecting that this might be a relevant pathway triggered downstream of Rbf, this group showed that a more potent form of Rbf, mutated at a putative caspase cleavage site, induced more widespread apoptotic cell loss, suppressible by knockdown of the single fly JNK homolog encoded by *bsk*.[4] A secondary consequence of the mutant Rbf-induced apoptosis was an abnormal, non-autonomous proliferative response, referred to as apoptosis-induced proliferation (AiP).[4] The AiP response was similarly dependent on JNK signaling. Regenerating a patterned tissue by compensatory proliferation after significant cell loss from apoptosis constitutes an essential homeostatic mechanism. Moreover, this experimental system now provided new opportunities to investigate the role of Rbf and downstream pathways in regenerative processes.

In this issue of Cell Cycle, Guenal and colleagues build on the phenotypic assays developed in previous work to decipher the complex *in vivo* regulation of JNK signaling specificity in response to Rbf-induced apoptosis.[5] As stated, the primary response to Rbf expression in proliferating *Drosophila* disc cells is JNK-dependent apoptosis, and secondarily, mutant Rbf stimulates non-autonomous JNK-dependent compensatory proliferation. How can JNK signaling direct these different cellular responses in the same tissue? The longstanding question of signaling specificity has, until recently, been difficult to address because of limitations in technologies to knock down multiple proteins simultaneously or tissue-specifically, difficulties in generating compound mutant tissues in sufficient quantity, and the sheer number of closely-related, possibly redundant, genes in large protein kinase families. Currently, multi-gene RNA interference techniques and sophisticated tissue-specific expression systems are making feasible the rapid dissection of pathway wiring in whole tissues and organisms. Clavier et al. apply these resources in *Drosophila* to illuminate the specific upper tier players in the JNK pathway, which mediate differential Rbf-induced responses.[5] Interestingly, they find that different adaptor/kinase combinations are selectively employed to drive JNK-dependent apoptosis and AiP. Their approach also teases apart remarkably well the 2 responses without the complication of producing 'undead' cells, as other groups have had to do by expressing p35 caspase inhibitor to prolong the period of apoptosis, effectively amplifying the AiP response. Ultimately though, the same downstream JNK and transcription factor effectors are activated, leaving us to scratch our heads again about mechanisms defining signaling specificity. Moving forward though, the opportunity arises to screen for additional effectors of Rbf-dependent tissue homeostasis. Sheriff Rb will certainly have more tales to tell around the campfire.

References

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