Human tumours have a high degree of cellular and genetic heterogeneity, and the mechanisms by which distinct mutations in different cellular clones may cooperate to promote tumorigenesis are unclear. Xu and colleagues present evidence that a two-tier mechanism involving Jun N-terminal kinase (JNK) and Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling enables interclonal cooperation between Ras^{G12V} and *scribbled* (*scrib*) mutations in *Drosophila melanogaster*.

Clones of genetically distinct cells can be created in *D. melanogaster* by induced mitotic recombination. Using this technique in the eye-antennal discs of *D. melanogaster* larvae, it has been shown that clones simultaneously expressing oncogenic Ras^{G12V} and harbouring loss-of-function mutations in the tumour suppressor *scrib* develop into large metastatic tumours (denoted $Ras^{G12V}scrib^{-}$). Remarkably, Wu *et al.* now show that invasive tumours similarly develop in eye-antennal discs containing Ras^{G12V} and $scrib^{-}$ mutations separately in adjacent clones (denoted $Ras^{G12V}//scrib^{-}$).

How do Ras^{G12V} and $scrib^{-}$ mutations cooperate when they occur in different cells? Microarray analysis and real-time reverse transcription PCR revealed upregulation of the unpaired (Upd) family of cytokines, which activate JAK–STAT signalling, in $Ras^{G12V}//scrib^{-}$ tumours. A dominant-negative form of the Upd receptor domeless, which mediates JAK–STAT activation, suppressed the growth and invasion of $Ras^{G12V}//scrib^{-}$ tumours, and clones co-expressing Ras^{G12V} and Upd cytokines developed into metastatic tumours. Ras and JAK–STAT signalling therefore seem to have synergistic effects on tumorigenesis.

So how are Upd cytokines upregulated in $Ras^{G12V}//scrib^{-}$ tumours? Previous evidence shows that JNK upregulates Upd in wounds and that increased JNK signalling occurs in $scrib^{-}$ clones. The authors therefore proposed that JNK activation in $scrib^{-}$ cells induces Upd upregulation. In support of this, wing discs doubly mutant for $scrib^{-}$ and the JNK kinase hemipterous (*hep*) had reduced activity of the JAK–STAT pathway. In addition, a dominant-negative form of the Jun kinase Basket (Bsk^{DN}) suppressed $Ras^{G12V}scrib^{-}$ tumours, but not Ras^{G12V}Upd tumours.

However, late-stage $Ras^{G12V}//scrib^{-}$ tumours mostly contain Ras^{G12V} cells and few $scrib^{-}$ cells. Therefore, JNK-dependent Upd upregulation in $scrib^{-}$ cells cannot fully account for tumour development. Indeed, Bsk^{DN} expression in Ras^{G12V} cells partially suppressed Upd upregulation and the growth of $Ras^{G12V}//scrib^{-}$ tumours. This suggests that JNK-induced Upd expression occurs in Ras^{G12V} as well as $scrib^{-}$ cells. Additionally, when wing discs were wounded in the anterior or posterior regions, JNK activity was observed across the whole disc. The authors therefore suggest that JNK activity in $scrib^{-}$ cells can propagate JNK activation in adjacent Ras^{G12V} cells. In this way, JNK-dependent Upd upregulation in Ras^{G12V}cells sustains tumour growth even when the original source of JNK activity, the $scrib^{-}$ cells, is no longer present.

As tissue damage has been linked to human tumorigenesis, it is intriguing that wounding in wing discs also cooperated with Ras^{G12V} to promote overgrowth. Together, these results highlight the importance of cell interactions in tumour development, and it will be of interest to determine whether similar cooperative mechanisms contribute to human cancers.

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ORIGINAL RESEARCH PAPER Wu, M *et al.* Interaction between Ras^{V12} and *scribbled* clones induces tumour growth and invasion. *Nature* **463**, 545–548 (2010)