Non-autonomous overgrowth by oncogenic niche cells: Cellular cooperation and competition in tumorigenesis

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Cancers progress through clonal evolution, the sequential acquisition of oncogenic mutations through Darwinian selection of advantaged subclones. For example, in colon cancers, adenomatous polyposis coli (APC) mutant clones acquire malignancy after further mutation of K-Ras, p53, and other genes. While genetic sequencing corroborated cancer’s clonal evolution, it also revealed remarkable clonal heterogeneity. A recent study found rampant intratumor genetic divergence, with ~60% of mutations not universally distributed among subclones. Furthermore, in human glioblastoma, coexisting subclones amplified distinct oncogenic receptor tyrosine kinases (epidermal growth factor receptor [EGFR], PDGFR, and c-Met). Clonal heterogeneity could therefore promote subclone cooperation alongside clonal competition. Indeed, interclonal cooperation between subclones potentiated tumorigenesis in mouse-modeled breast cancer. Excitingly, clonal population dynamics of cancer-derived, heterogeneous subclones were reproducible across independent xenografts, suggesting that tumor heterogeneity is a tractable problem. While interclonal communication is considered crucial to cancer’s etiology, detailed in vivo mechanisms are lacking.

Drosophila genetics enables manipulation of oncogenic cell clones in vivo. Remarkably, Drosophila tumorigenesis recapitulates aspects of human cancer, including polarity loss, basement-membrane degradation, and invasion. Accordingly, genetic screens in Drosophila have identified evolutionarily conserved tumor-suppressor genes, including Hippo pathway components. Genetic mosaic analysis also revealed an unusual tumor-promoting cell population that can be called “oncogenic niche cells” (ONCs). Oncogenic niche cells drive non-autonomous tumor progression through cellular competition and cooperation with surrounding cell populations. This review characterizes diverse ONCs identified in Drosophila and describes the genetic basis of non-autonomous tumor progression. Similar mechanisms may contribute to mammalian cancer progression and recurrence.
by cell competition, a process in which normally viable "loser" cells are eliminated by neighboring "winner" cells. Cell competition is triggered by lower translation rates, disrupted apico-basal polarity, or aberrant signal transduction, and thus functions as a tumor suppressor and developmental regulator. \(13-16\)

Alongside cell competition, ONCs commonly feature cooperation between the JNK and Hippo pathways. Below, we describe five classes of ONCs characterized in \textit{Drosophila} imaginal epithelia.

**Oncoprotein Src.** Elevation of oncoprotein Src often correlates with tumor malignancy, yet Src’s role in tumorigenesis remains unclear. \(17\) Clones of cells overexpressing Src64B (Src; c-Src homolog) in the \textit{Drosophila} imaginal disc are eliminated by JNK-dependent cell competition. \(18,19\) However, Src clones also function as ONCs to cause non-autonomous overgrowth of surrounding tissue (Fig. 1b). \(19\) Src-activated cells accumulate intracellular F-actin and activate the Hippo pathway effector Yorkie (Yki; YAP homolog). Simultaneously, JNK signaling induces cell death in a cell-autonomous manner but propagates Yki to neighboring cells, causing overgrowth of surrounding tissue (Fig. 1c). Blocking Yki inside Src-activated cells abolished neighboring Yki activation, implying propagation of Yki from ONCs. Thus, while JNK-mediated cell competition restrains Src-activated ONC autonomous growth, JNK–Yki cooperation contributes to non-autonomous tumorigenesis.

**Endocytic dysregulation.** Endocytic trafficking controls internalization and sorting of extracellular molecules and transmembrane proteins. Consequently, endocytic dysregulation disrupts signaling pathways and cell polarity, contributing to human cancers. \(20-22\) Multiple genetic screens in \textit{Drosophila} identified endosomal sorting complex components vps25 and erupted (ept; tsg101 homolog) as causing non-autonomous overgrowth. \(23-26\) Endocytic ONCs accumulated endosomal Notch, inducing the cytokine Unpaired (Upd; interleukin [IL]-6 homolog) and triggering JAK–signal transducer and activator of transcription (STAT) signaling in surrounding cells (Fig. 2a). A similar but distinct endocytic ONC was formed by mutating Rab5, an early endosome component. Rab5-deficient ONCs accumulated EGFR and Eiger (tumor necrosis factor homolog), activating Ras and JNK pathways, respectively. \(27\) JNK and Ras signaling cooperatively activated Yki, inducing...
Upd expression and subsequent non-autonomous overgrowth (Fig. 2b). Non-autonomous phenotypes are dependent on cell competition; 

\[ p53 \text{-} \text{expressing cells prevented from dying autonomously overgrow, (28) } \]

suggesting apoptosis propagated by Eiger

\[ \text{Rab5DN} \text{-expressing cells clones autonomously overgrow, (28) suggesting} \]

that establishment of endocytic ONCs is contingent on cell competition and clone size.

**Apoptotic stimulus.** Apoptosis is a hallmark of many cancers and often correlates with increased proliferation and worse prognosis (29). In Drosophila wing discs, massive cell death triggers non-autonomous “compensatory proliferation”, yielding normal adult wings. (30) Yki is activated in dying and neighboring cells and is essential for wing disc regeneration. (31, 32) Notably, in this case, JNK activation is necessary and sufficient for Yki induction in wing discs, (31) and JNK activity non-autonomously propagates following local wounding. (33) JNK also stimulates cell migration to the wound site, similar to JNK-driven developmental or tumorigenic invasion (Fig. 3a). (35, 36)

In a similar phenomenon, when cell death is induced but not executed, typically through overexpression of caspase inhibitor p35, persistent “undead” cells become ONCs and trigger non-autonomous overgrowth through the growth factors Decapentaplegic (Dpp; bone morphogenetic protein/transforming growth factor-\( \beta \) homolog) and Wingless (Wg; Wnt homolog). (37) In wing discs, this is dependent on a p53-JNK positive feedback loop activated by the initiator caspase Dronc (Fig. 3b). (40)

Undead cells generated through genomic instability also function as ONCs, secreting Wg and triggering JNK-dependent non-autonomous hyperplasia. (41) Here, JNK-activated MMP1 activity also induces basement membrane degradation and invasion. Intriguingly, undead cells can also cause non-autonomous apoptosis propagated by Eiger-JNK. (42) Dying ONCs may unleash an autocatalytic wave of JNK, death, growth factor secretion, and proliferation.

**Polarity loss.** Apico-basal polarity is essential for epithelial cell function and homeostasis. Polarity loss underlies many cancers and is often critical for cancer progression. (43) Imaginal epithelia entirely mutant for conserved apico-basal polarity genes scribble (scrib) or discs large (dlg) develop into tumors. However, clones of these mutant cells surrounded by wild-type cells are eliminated through Eiger-JNK signaling in “tumor-suppressive cell competition”. (44) Competition-induced JNK also suppresses Yki activity in scrib clones. (45) Although JNK restrains overgrowth of scrib tissue, it is required for tumor progression and metastasis of scrib+RasV12 clones. (46) Surprisingly, distinct scrib and RasV12 mosaic clones induced in the same imaginal disc still trigger metastasis of RasV12 cells. (33) suggesting that scrib cells function as ONCs (Fig. 4a). JNK activity propagates from scrib to RasV12 cells, inducing Upd and JAK–STAT signaling that cooperates with Ras signaling to induce metastasis. Remarkably, JAK–STAT signaling is also required within scrib-neighboring cells to eliminate scrib clones. (33, 46) As JAK–STAT and JNK both suppress and promote scrib tumor formation, competition-triggered interclonal cooperation likely underlies polarity-defective ONCs.

**Ras, mitochondrial dysfunction, and senescence.** Metastasis of RasV12-expressing cells can be triggered by different ONCs, such as scrib clones. (8, 47) A genetic screen for RasV12-induced non-autonomous growth identified mutations in genes required for mitochondrial respiratory function, which are frequently downregulated in various cancers. (48) Clones harboring RasV12 and mitochondrial dysfunction (RasV12/mito–/–) produce reactive oxygen species (ROS), activating JNK. JNK and Ras cooperatively activate Yki, which upregulates Upd and Wg to induce surrounding tissue overgrowth. (49) Thus, RasV12/mito–/– cells act as ONCs. Interestingly, RasV12/mito–/– cells cause cell-cycle arrest through ROS production and undergo p53-dependent cellular senescence (Fig. 4a). (50) Overexpression of p53 inside RasV12 clones is sufficient to induce ONCs and non-autonomous overgrowth. Therefore, senescent cells may function as ONCs through inflammatory cytokine release. (51) A conserved phenomenon called the senescence-associated secretory phenotype (SASP). (52) Indeed, paralleling scrib interclonal cooperation, RasV12/mito–/–-produced Upd triggers adjacent RasV12 metastasis (Fig. 4b). (49) Interestingly, activated Ras signaling stimulates Eiger exocytosis, causing JNK accumulation and JAK–STAT activation at clonal boundaries between RasV12 and wild-type cells. (53) JNK transcytosis could underlie JNK propagation and cell competition’s role in oncogenic cooperation.

**Oncogenic niche cell themes: JNK-mediated cell competition and cooperation**

There are several shared ONC themes (Table 1). Notably, Src-activated, endocytic, and polarity-defective ONCs undergo JNK-mediated cell competition. Thus, tumor-suppressive cell
Although JNK impinges on Hippo through Ajuba-mediated Warts regulation, activating Yki and driving overgrowth, (55,56) non-autonomous JNK does not induce Yki. Instead, autonomous JNK cooperatively propagates Yki activity to neighboring cells (Fig. 1c). (19) Additionally, polarity loss can still induce non-autonomous Yki activation in tissues lacking the JNK ligand Eiger, (45) suggesting that JNK-independent pathways may activate non-autonomous Yki in polarity ONCs. Thus, specific mechanisms of non-autonomous Yki activation remain unclear. Surprisingly, JNK directly impinges on Hippo through Ajuba-mediated Warts regulation, activating Yki and driving overgrowth. (55,56)

Table 1. Common oncogenic niche cell (ONC) themes

| ONCs                  | Competition and cell death | Cooperation | Growth factors | Cellular senescence or p53 accumulation (p53+?) |
|-----------------------|----------------------------|-------------|----------------|-----------------------------------------------|
| Src-activated JNK     | JNK→cell death             | JNK→Yki    |                |                                               |
| Endocytic dysregulation | JNK→cell death           | Notch→JAK→STAT | Upd         | p53+                                          |
| Apoptotic stimulus    | Cell death                 | JNK→Dpp, Wg | Wg             | p53+                                          |
| Polarity defect       | JNK→cell death             | JNK→JAK→STAT | Upd         |                                               |
| RasV12/mito−/−        | JNK→JAK→Yki               | JNK/Ras→Yki | Dpp            |                                               |
|                       |                            | JNK→Yki    | Wg             |                                               |
|                       |                            | JNK→p53    |                |                                               |

Dpp, Decapentaplegic; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; Upd, UNPAIRED; Wg, Wingless; Yki, Yorkie.

Fig. 4. Cooperation between RasV12 and oncogenic niche cells (ONCs). (a) scrib cells activate Eiger/JNK signaling, causing neighboring RasV12 cells (purple) to secrete Unpaired (Upd) and metastasize. Alternatively, RasV12/mito−/−cells (mitochondrial dysfunction, senescent ONC) generate reactive oxygen species (ROS) and activate p53, which cooperatively activate JNK. JNK and RasV12 inactivate the Hippo pathway, activating Yorkie (Yki) and triggering secretion of Upd and Wingless (Wg). ONC-induced senescence-associated secretory phenotype stimulates neighboring RasV12 cell invasion. (b) While RasV12 clones (GFP+) fail to metastasize from the larval brain hemisphere (BH) to the ventral nerve cord (VNC), senescent ONCs (RasV12/mito−/−) stimulate RasV12 invasion (arrowheads). STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor.
core Hippo pathway components are not commonly disrupted in human cancer. Instead, Hippo dysregulation may potentiate tumorigenesis through interclonal cooperation. Indeed, Yki/YAP is nuclear in ~60% of hepatocellular carcinomas and 65% of non-small-cell lung cancers. Oncogenic niche cell-driven, non-autonomous Yki activation could contribute to mammalian cancer progression.

JNK may additionally act through Polycomb group proteins (PcG), which enforce epigenetic repression. During wound-healing, JNK inactivates PcG to allow fate reprogramming. Therefore, JNK activity could alleviate PcG repression of growth factors like Wg or Upd. Notably, loss of PcG protein Polyhomeotic causes non-autonomous, Upd-mediated overgrowth. Because mammalian JNK can act as a pro-apoptotic gene linked to tumor regulation, JNK may function in both mammalian and Drosophila ONCs.

Oncogenic niche cell hypothesis: Crumbs in ONC establishment

A common ONC theme is cooperative Yki activation (Table 1), suggesting that Hippo pathway activity may influence ONCs. Indeed, differential Hippo pathway activity triggers cell competition: Yki-activated cells are super-competitors while yki mutants are eliminated. Alongside JNK-based competition, could Hippo-mediated competition establish ONCs? The apical transmembrane protein Crumbs (Crb) is a good candidate for ONC establishment. Crb recruits Expanded (Ex), activating Hippo and inhibiting Yki. Intriguingly, Crb accumulates in polarity and endocytic ONCs. Furthermore, Crb-overexpressing clones are eliminated while crb mutants induce neighbor-cell death in a competitive phenomenon dependent on Crb-Crb extracellular interactions. Therefore, in certain
ONCs, high Crb may may JNK-dependent repression of Yki and "loser" status. Conversely, neighboring cells with lower Crb would overgrow through JNK-activated Yki. Crb3 is downregulated in human tumor-derived cell lines, consistent with lower Crb permitting overgrowth.

However, while Crb-overexpressing cells are eliminated, overexpression of only Crb’s intracellular domain (Crb-intra) causes autonomous overgrowth. Intriguingly, Crb-intra overgrowth is rescued by depletion of Eiger’s receptor Grindelwald, which colocalizes with Crb at apical membranes. This supports the idea that Crb-JNK might contribute to ONCs, but highlights the complexity of Crb overexpression phenotypes. Indeed, although Crb recruits Ex and activates Hippo, Crb can also promote Ex degradation through ubiquitylation. Moreover, Hippo pathway mutants accumulate Crb yet become super-competitors, perhaps through elevation of anti-apoptotic DIA1 or mechanisms paralleling Crb-intra induced overgrowth. While Crb’s contribution to ONCs is highly complex, it is likely that Crb and JNK can cooperatively dictate Yki activity and competitive outcomes in ONCs.

Oncogenic niche cell themes: a role for cellular senescence?

Though cell death is common to ONCs, it is not induced in RasV12/mito−/− cells, which instead activate p53 and undergo cellular senescence. JNK-activated Yki stimulates Upd/Wg secretion in a SASP, reminiscent of growth factor secretion by “undead” ONCs. Intriguingly, p53 has been linked to cell competition. In murine hematopoietic stem cells (HSCs), irradiated p53−/− HSCs outcompete p53+/− but not p53+/− HSCs. Separately, p53 knockdown in differentiared murine tissue allowed disproportionate expansion of p53−/− cells. Surprisingly, p53 knockdown in undifferentiated embryonic stem cells lead to p53−/− cell elimination, suggesting that p53 knockdown triggers context-dependent cell competition. Supporting this, apoptosis of Myc-overexpressing, p53−/− Drosophila cells was dependent on surrounding neighbors. Furthermore, p53 is intimately linked to JNK in Drosophila: p53 and JNK form a feed-forward loop in undeand ONCs, sufficient to induce each other’s expression and p53 directly binds JNK. Indeed, blocking p53 in RasV12/mito−/− abrogated JNK activity and ONC formation.

Therefore, p53 or cellular senescence may trigger cell competition and establish ONCs. p53 is elevated in tsq101 null mice, likely from impaired ubiquitin-mediated degradation. Ubiquitinated proteins accumulate in vps25 and ept mutant ONCs, and mutations in an E1 ubiquitin-activating enzyme cause non-autonomous overgrowth. While these phenotypes can partly be explained by p53’s pro-apoptotic role, p53 may fuel non-autonomous tumor progression through cell competition and SASP. As p53 is frequently mutated in human cancers, dysregulated cell competition or SASP may contribute to mammalian cancer progression (see below).

Oncogenic niche cells in mammalian cancer

Do ONCs contribute to mammalian cancer progression? Although cellular senescence can suppress tumor formation, it can fuel non-autonomous overgrowth through cytokine secretion in a SASP. Mammalian studies also suggest that SASP can drive non-autonomous tumor progression. Senescence-associated secretory phenotype of murine hepatic stellate cells potentiates hepatocellular carcinoma formation. Moreover, SASP in epithelial cells triggers malignancy through paracrine secretion of IL-6 and IL-8, paralleling senescent ONCs’ induction of neighboring RasV12 metastasis (Fig. 4b). Thus, non-autonomous tumor progression through cellular senescence and SASP seems conserved in mammalian cancer progression. Like cell competition, cellular senescence can suppress or promote tumorigenesis. As chemotherapy often potentiates cellular senescence, senescence ONCs could contribute to cancer recurrence (Fig. 5).

Alongside cellular senescence, cell death is commonly observed in human cancers and often correlates with increased tissue proliferation. In a mouse model of hepatocellular carcinogenesis, dying hepatocytes activate JNK and ROS, inducing proliferation of surrounding cells through cytokine release. Importantly, therapy-induced death can also trigger ONC-mediated proliferation. Following radiotherapy, dying cancer cells activate effector caspases 3/7, triggering prostaglandin E2 (PGE2) secretion. Subsequently, PGE2 stimulates neighbor-cell proliferation. Notably, tumor recurrence positively correlated with high activation of caspases 3/7 in human patients. In human prostate cancer, chemotherapy-induced PGE2 can trigger non-autonomous cell proliferation and tumor repopulation through cancer stem cell populations (see below). Thus, cell death and cellular senescence in ONCs can initiate tumors and hinder treatment (Fig. 5).

Oncogenic niche cells may promote tumorigenesis through non-autonomous effects on cancer stem cells (CSCs). The CSC hypothesis proposes that specialized stem cells contribute disproportionately to cancerous populations. Consequently, cancer heterogeneity can be partially attributed to differentiation hierarchies stemming from distinct CSC subpopulations. Experimental evidence suggests that CSC progeny are surprisingly plastic in their fate and can dedifferentiate to CSCs. Intriguingly, a pulse of Sre activity was sufficient to convert a non-malignant breast cell line into a self-renewing, containing cancer through an IL-6/nuclear factor-κB positive feedback loop. Furthermore, IL-6 addition to regular cancer cells induced dedifferentiation to CSCs. As ONCs frequently induce Upd/IL-6 (Table 1) through JNK–Yki cooperation in Drosophila, ONC-secreted factors could promote non-autonomous CSC induction. Concomitantly, ONCs could promote CSC proliferation, such as in therapy-induced CSC proliferation and repopulation. Notably, in human hepatocellular carcinoma, JNK and IL-6 markers are commonly associated with CSCs, although no evidence directly links CSCs to ONCs. Additionally, as CSCs are often resistant to apoptosis, it is possible that CSCs themselves could function as “undead” ONCs when challenged with apoptotic stimuli, such as chemotherapy.

Conclusions

Drosophila studies have brought insight to tumor progression through genetic dissection of ONCs. As senescent and dying ONCs are likely conserved in mammals, further ONC analysis will inform our understanding of mammalian cancer etiology. Despite diverse genetic triggers, ONCs share many characteristics, including cell death, competition, and cooperation. The role of JNK in cell competition and its cooperation with Yki merits further study in both Drosophila and mammalian cancer models. The relationships between ONCs, Crb, p53, cellular senescence, and cell competition are exciting areas for future
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16 Baker NE. Cell competition. 15 de Beco S, Ziosi M, Johnston LA. New frontiers in cell competition. Chemotherapy-induced death or senescence. Therefore, cancer and apoptosis. We envision that ONCs contribute to non-autonomous tumour initiation and progression through cooperation with adjacent premalignant tissue or through CSC induction or stimulation (Fig. 5). The basic genetic mechanisms uncovered in Drosophila ONCs likely underlie interclonal cooperation in heterogeneous mammalian cancers. Moreover, mammalian evidence suggests that ONCs fuel tumour recurrence following chemotherapy-induced death or senescence. Therefore, cancer topography, the potential for ONC induction or subclone cooperation, must be carefully considered before individualized therapies become a reality.

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