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Review

It takes two to tango, a dance between the cells of origin and cancer stem cells in the *Drosophila* larval brain

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ABSTRACT

During malignant transformation the cells of origin give rise to cancer stem cells which possess the capacity to undergo limitless rounds of self-renewing division, regenerating themselves while producing more tumor cells. Within normal tissues, a limitless self-renewal capacity is unique to the stem cells, which divide asymmetrically to produce more restricted progenitors. Accumulating evidence suggests that misregulation of the self-renewal machinery in stem cell progeny can lead to tumorigenesis, but how it influences the properties of the resulting tumors remains unclear. Studies of the type II neural stem cell (neuroblast) lineages in the *Drosophila* larval brain have identified a regulatory cascade that promotes commitment to a progenitor cell identity by restricting their response to the self-renewal machinery. *Brain tumor* (Brat) and Numb initiate this cascade by asymmetrically extinguishing the activity of the self-renewal factors. Subsequently, *Earmuff* (Erm) and the SWI/SNF complex stably restrict the competence of the progenitor cell to respond to reactivation of self-renewal mechanisms. Together, this cascade programs the progenitor cell to undergo limited rounds of division, generating exclusive differentiated progeny. Here we review how defects in this cascade lead to tumor initiation and how inhibiting the self-renewal mechanisms may be an effective strategy to block CSC expansion.

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1. Introduction

Investigation of the mechanisms by which cancers are formed and regulated may aid in the development of more effective cancer therapies [1,2]. Accumulating evidence suggests that aberrant activity of stem cell self-renewal pathways can transform progenitor cells into tumor initiating cells [3–11]. In addition, aberrant

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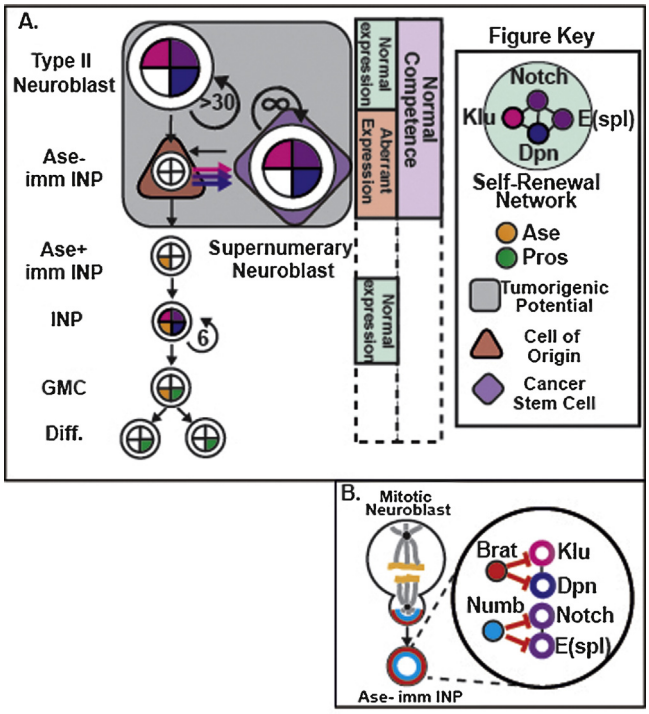

Fig. 1. Aberrant expression of self-renewal factors causes uncommitted progenitors to revert to form CSCs. (A) Lineage diagram depicting tumorigenesis resulting from overexpression of self-renewal factors or *brat* or *numb* mutation. Type II neuroblasts express a self-renewal network (light blue) that includes Notch (purple), E(spl)mγ (purple), Dpn (blue), and Klu (magenta). Ase⁻ immature INPs remain competent (light purple box) to respond to aberrant expression (salmon box) of the self-renewal factors and can revert to form supernumerary neuroblasts. In these tumor types, Ase⁻ immature INPs act as the cell of origin (brown triangle) and supernumerary neuroblasts are likely the CSCs (purple diamond); these cell types retain tumorigenic potential (gray box). In contrast, INPs do not retain tumorigenic potential in these tumor types, and only divide 5–6 times to generate exclusively GMCs and differentiated cells that express nuclear Pros (green). (B) Brat and Numb repress expression of self-renewal factors in Ase⁻ immature INPs. (Left) Schematic depicting the mitotic division of a type II neuroblast showing: Brat (red) and Numb (blue) are basally segregated into the Ase⁻ immature INP; DNA is shown in yellow; spindle in gray; and centrosomes in black. (Right) Once in the Ase⁻ immature INPs, Brat and Numb act in parallel to inhibit aberrant expression of distinct components of the self-renewal network.

activity of stem cell self-renewal pathways has also been implicated in the regulation of the cancer stem cell (CSC) types that support long term tumor growth [12–18]. These CSCs are defined by their capacity to self-renew while producing a hierarchical lineage of cells that either differentiate and become non-tumorigenic or form more CSCs to expand the tumor [19,20]. How different oncogenic lesions coerce non-stem cell types into aberrantly responding to the self-renewal machinery and initiating tumor formation, and how this contributes to the regulation of the resulting CSCs remains unclear.

The type II neuroblast lineage in the *Drosophila* larval brain serves as an exceptional *in vivo* model to study the regulation of progenitor cells during normal development and tumorigenesis [21–23]. A type II neuroblast undergoes repeated rounds of asymmetric division to self-renew and to produce uncommitted (immature) intermediate neural progenitors (INPs) that are transiently arrested in the cell cycle progression (Fig. 1A) [24–26]. Following division, the expression of the self-renewal factors remains on in the type II neuroblast but is asymmetrically extinguished in the immature INP [27–29]. The immature INP then undergoes a series of maturation steps to commit to the functional identity of an INP [28,30,31]. Subsequently, INPs reactivate expression of neuroblast self-renewal factors, but their response is severely restricted, ensuring INPs only undergo five-to-six rounds of asymmetric division to exclusively generate ganglion mother cells (GMC) and differentiated cells [32] (Fig. 1A). A series of recent studies have demonstrated that defects in restricting the responses to self-renewal factors in immature INPs or INPs allows them to aberrantly reacquire a neuroblast like identity [27,28,31,33–36]. This leads to the formation of massive numbers of supernumerary neuroblasts that act as CSCs, forming metastatic tumors that can be serially propagated upon transplantation into adult hosts [34,37]. In this review, we will discuss how different mutations lead to aberrant responses to the self-renewal factors, resulting in different cells types acting as the cell of origin and producing CSCs with distinct properties. In addition, we will discuss how by modifying the aberrant responses to self-renewal factors, it may be possible to specifically interfere with the inter-conversion of progenitors to a less restricted stem cell type, thereby preventing tumor growth.

2. Aberrant reversion of uncommitted progenitor cells induced by self-renewal factors leads to the formation of tumor-initiating cells

Studies from several groups have collectively established a network of factors that plays critical roles in promoting the self-renewal of type II neuroblasts (Fig. 1A) [28,29,34,38]. Consistent with aberrant responses to self-renewal factors promoting tumor formation, over-expression of components of this self-renewal network triggers formation of massive numbers of supernumerary neuroblasts that are tumorigenic [34]. A highly conserved component of the type II neuroblast self-renewal network is *Notch*, which encodes a transmembrane protein [39,40]. Upon proteolytic activation, the Notch intra-cellular domain (NICD) translocates to the nucleus where it complexes with the DNA binding protein Suppressor of Hairless (Su(H)) to activate target gene expression. *Notch* is indispensable for the maintenance of type II neuroblasts, and over-expression of the *NICD* in type II neuroblast lineages leads to supernumerary neuroblast formation [28,41]. Thus, *Notch* is both necessary and sufficient to promote type II neuroblast self-renewal. *Notch* promotes the self-renewal of type II neuroblasts in part by directly regulating the expression of *Enhancer of split mγ* (*E(spl)mγ*), which encodes a basic helix-loop-helix-Orange transcription factor [29] (Fig. 1A). Removing *Notch* function abrogates the expression of the *E(spl)mγ-gfp* reporter transgene in all neuroblasts, and loss of the *E(spl)* locus renders over-expression of the *NICD* unable to induce supernumerary type II neuroblast formation. Although over-expression of *E(spl)mγ* in type II neuroblast lineages induces supernumerary neuroblast formation, loss of the *E(spl)* locus does not affect the maintenance of type II neuroblasts [29,34]. Thus, *E(spl)mγ* is only sufficient to promote neuroblast self-renewal, suggesting that additional parallel mechanisms must exist. Similar to *E(spl)mγ*, over-expression of *deadpan* (*dpn*), which also encodes a basic helix-loop-helix-Orange transcription factor, in type II neuroblast lineages also induces supernumerary neuroblast formation, but loss of *dpn* function does not affect the maintenance of type II neuroblasts [34,38,42]. Most importantly, type II neuroblasts lacking both *dpn* and the *E(spl)* loci rapidly undergo premature differentiation, indicating that Dpn and E(spl)mγ function cooperatively to maintain the self-renewal of type II neuroblasts [29] (Fig. 1A). Despite containing many functional Su(H) binding sites in the regulatory region, the expression of Dpn does not require *Notch* function, and *dpn* is dispensable for supernumerary neuroblast formation induced by over-expression of *NICD* [29]. Therefore, Dpn functions in parallel with E(spl)mγ to regulate the self-renewal of type II neuroblasts possibly by integrating multiple upstream signaling inputs including Notch (Fig. 1A).