

cNeoblast Specialization

The use of an adult population of pluripotent stem cells to fuel planarian regeneration presents several important questions. Is this population heterogeneous, or is it derived from a single pluripotent population, as clonal studies (see Figure 24.19) suggest is possible? Moreover, what is the process whereby a neoblast can create the 30 or so cell types of the adult planarian? When does cell specification take place? Could it be that lineage-restricted multipotent stem cells are derived from a cNeoblast and are seeded throughout the flatworm prior to any injury? Or are differentiated postmitotic cells produced directly from a pluripotent neoblast at the time of injury (Figure 1)?

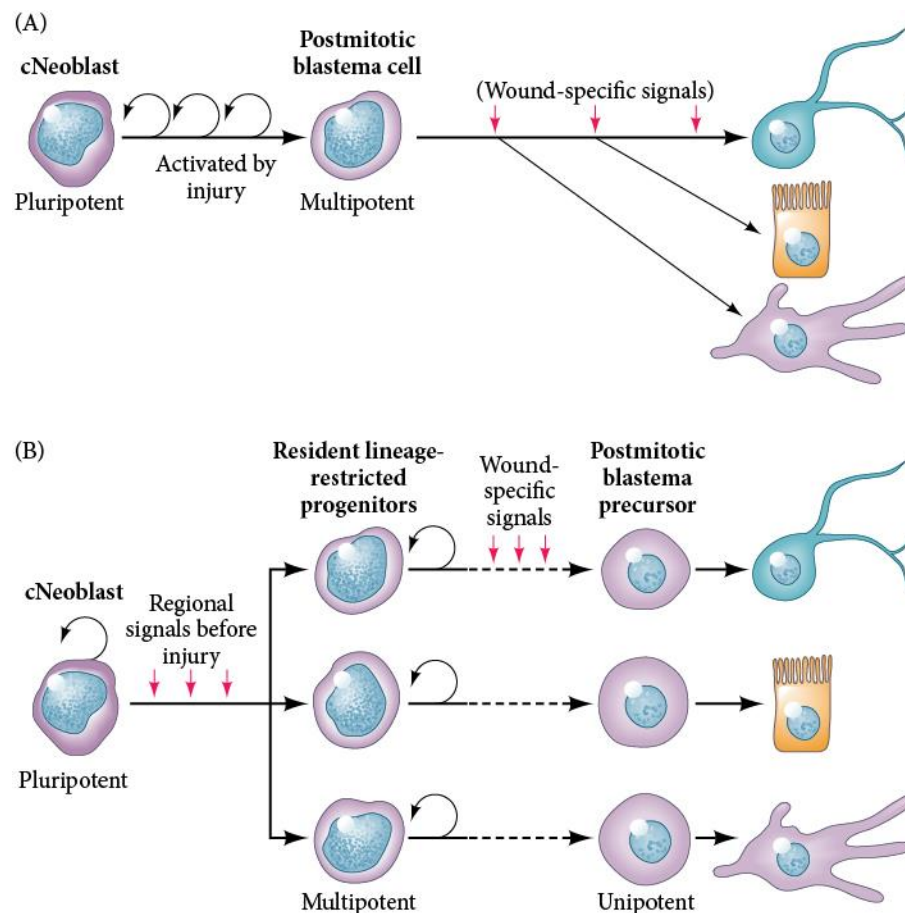
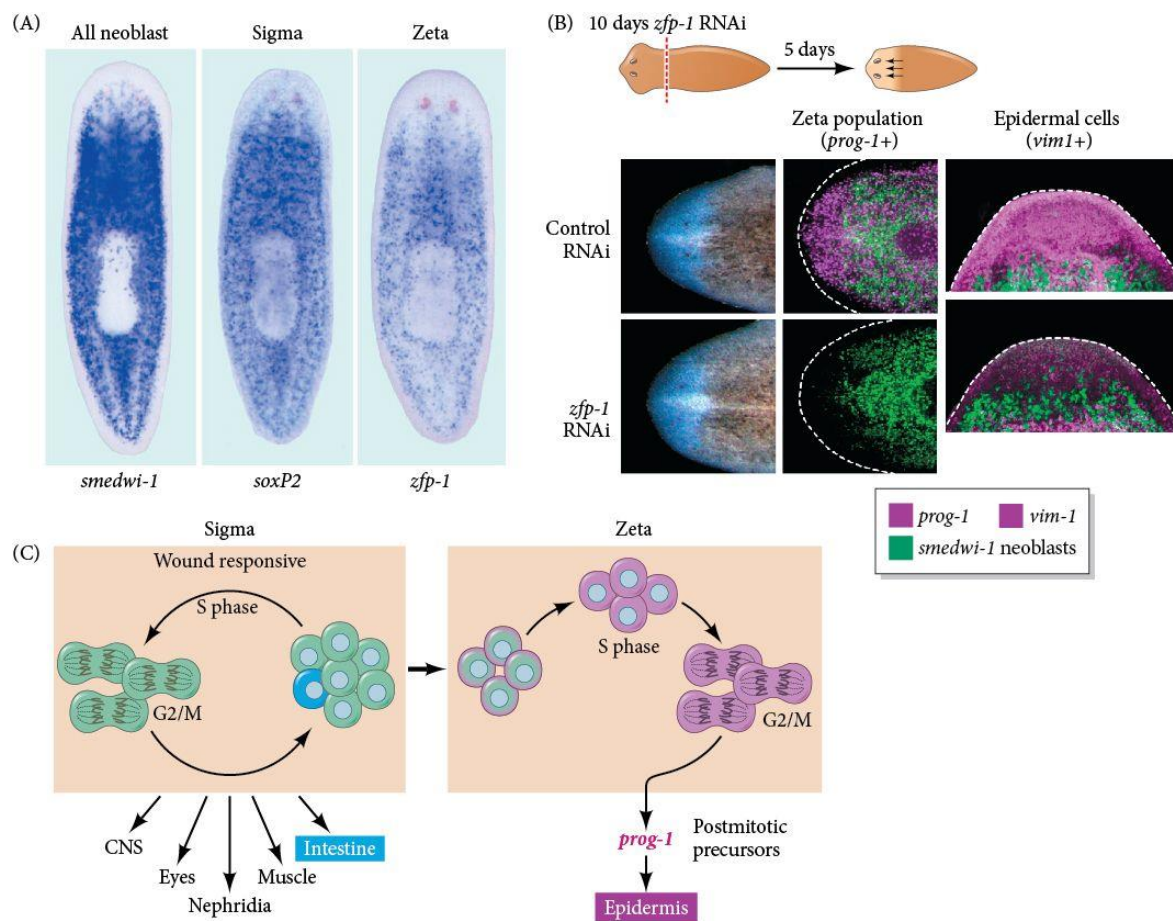


Figure 1 Two possible mechanisms for neoblast specification during regeneration. (A) One proposed mechanism is that a single pluripotent neoblast is responsible for generating new cell progenitors that form the multipotent cells of the blastema. (B) Alternatively, multipotent progenitor cells are positioned throughout the planarian with their lineages specified based on their position. These divide and produce postmitotic blastema cells that differentiate into their specified fates.

Genetic studies are beginning to unravel some of the answers. The gene *smedwi-1* is expressed by all neoblasts and has become the most common marker for their identification across planarian

species (Reddien et al. 2005; Reddien 2013). Several studies have revealed that some neoblasts express different sets of transcription factors that correlate with specific cell fates in the planarian adult, which suggests that lineage specification of stem cell populations may exist in the organism for normal development and in response to injury (Hayashi et al. 2010; Pearson et al. 2010; Shibata et al. 2012). To further investigate this possibility, the Reddien lab performed transcriptomic analysis of individual neoblasts during homeostasis and regeneration (van Wolfswinkel et al. 2014). Through this comprehensive analysis, the researchers found that two distinct populations of neoblasts exist, which they named zeta and sigma (Figure 2A). Although zeta and sigma neoblasts are morphologically indistinguishable, they have several defining characteristics: they express different gene regulatory networks, and zeta neoblasts are postmitotic, whereas sigma neoblasts are highly proliferative and are the only stem cells directly responsive to injury. Upon amputation, sigma neoblasts (*soxP2*-expressing) generate a huge variety of cell types (brain, intestine, muscle, excretory, pharynx, and eyes), as well as the progenitor population for zeta neoblasts. Zeta neoblasts (*zfp-1*-expressing) are then directly responsible for creating the remaining epidermal cell types. Planarians lacking a zeta population can be made through *zfp-1* RNAi knockdown. When the heads of these planarians were amputated, the sigma neoblasts were able to fuel the regeneration of all the cells of new heads, except for the epidermal lineages (Figure 2B and C; van Wolfswinkel et al. 2014). These data all support a vital role for stem cells in regeneration. But we are still left with the question, How are the specific cell types patterned correctly? How does the flatworm tell the posterior blastema to become tail and the anterior blastema to become head?



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Figure 2 Two distinct populations of neoblasts exist, with one of them responsive to injury. (A) In situ hybridizations marking (blue) all neoblast cells (*smedwi-1*; left); the sigma neoblast population (*soxP2*; center); and the zeta neoblast population

(*zfp-1*; right). (B) Planarian heads largely regenerate even in the absence of zeta neoblasts (leftmost, brightfield photos). Loss of the zeta population by RNAi is indicated by a lack of *prog-1* expression (center photos) as seen with fluorescence in situ hybridization (FISH). Although, epidermal cell types (right) do not fully regenerate in the absence of zeta neoblasts (*vim-1*, purple), the remaining neoblasts (green; likely sigma) and their derived cell types are unaffected. (C) Model of sigma neoblast-led development and regeneration. Sigma neoblasts direct the generation of numerous cell types as well as the zeta progenitor cells. Zeta neoblasts give rise to epidermal cell fates through a *prog-1*-positive postmitotic precursor state.

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