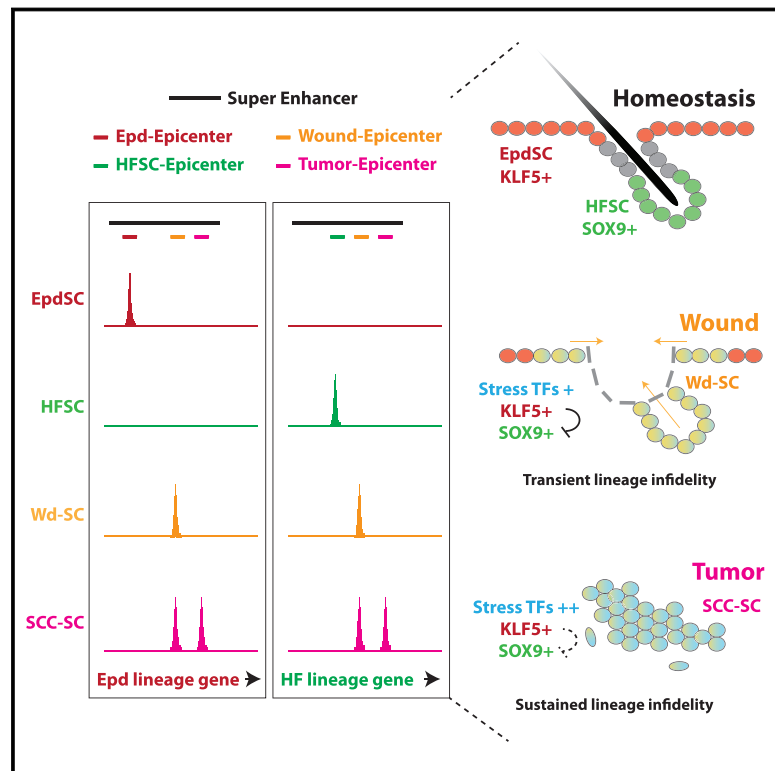


Stem Cell Lineage Infidelity Drives Wound Repair and Cancer

Graphical Abstract



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In Brief

Stem cell lineage infidelity occurs transiently in wounds and persists in cancer, driving wound repair and malignancy.

Highlights

- Stem cell lineage infidelity occurs transiently in wounds and persists in cancer
- Wounds and cancer converge on lineage infidelity irrespective of stem cell origin
- Lineage infidelity is governed by stress-induced transcription factors
- Activation of oncogenic enhancers distinguishes cancer from wounds



Stem Cell Lineage Infidelity Drives Wound Repair and Cancer

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<http://dx.doi.org/10.1016/j.cell.2017.03.042>

SUMMARY

Tissue stem cells contribute to tissue regeneration and wound repair through cellular programs that can be hijacked by cancer cells. Here, we investigate such a phenomenon in skin, where during homeostasis, stem cells of the epidermis and hair follicle fuel their respective tissues. We find that breakdown of stem cell lineage confinement—granting privileges associated with both fates—is not only hallmark but also functional in cancer development. We show that lineage plasticity is critical in wound repair, where it operates transiently to redirect fates. Investigating mechanism, we discover that irrespective of cellular origin, lineage infidelity occurs in wounding when stress-responsive enhancers become activated and override homeostatic enhancers that govern lineage specificity. In cancer, stress-responsive transcription factor levels rise, causing lineage commanders to reach excess. When lineage and stress factors collaborate, they activate oncogenic enhancers that distinguish cancers from wounds.

INTRODUCTION

Human adult tissues harbor resident stem cells (SCs) responsible for homeostasis and wound repair. Tumorigenesis arises when normal SCs accumulate mutations that cause them to derail, shifting their homeostatic balance to favor tissue growth at the expense of differentiation. In contrast to wound repair, where the growth: differentiation imbalance is transient, cancers are refractory to tissue restoration cues, seemingly hijacking these normal cellular programs to fuel their molecular thirst for uncontrolled growth.

The notion that a “cancer is a wound that never heals” has origins dating back to Rudolf Virchow in the 1800s. Since then, tantalizing parallels between cancer and wounds have emerged in many contexts (Antsiferova and Werner, 2012; Arwert et al., 2012; Dvorak, 1986). For instance, it has long been recognized that human patients suffering from chronic wounds have increased susceptibility to cancers (Dunham, 1972; Haddow,

1972). Additionally, mice with gene mutations that enhance skin SC activity heal wounds faster but also become more susceptible to squamous cell carcinomas (SCCs) (Guasch et al., 2007; Hance et al., 2014). By contrast, mice whose skin possesses mutations that impede SC activation display reduced efficiency in wound closure but increased resistance to cancers (Schober and Fuchs, 2011).

Intimate connections between wounds and tumors have also been drawn at the molecular level. Following serum stimulation, cultured fibroblasts elicit a robust wound repair signature resembling that of certain human carcinomas and predictive of poor patient prognosis (Chang et al., 2004; Iyer et al., 1999). Gene profiling studies in various wounded and tumorigenic epithelial tissues have further highlighted a concordant gene signature (Pedersen et al., 2003; Riss et al., 2006). Although intriguing, it remains unclear which of the normal SC remodeling pathways are exploited by tumor SCs and how cancers rewire pre-installed regulatory networks to support malignancy. The answers could be important in devising new and improved therapeutics for treatments of chronic wounds as well as cancers.

Mouse skin offers an excellent genetically tractable model system to tackle these issues. Its epithelium has two distinct lineages, hair follicle (HF) and epidermis (Epd), each harboring their own resident SCs (Fuchs, 2016). HFSCs reside in a region of the follicle known as the bulge, and during normal homeostasis, their role is to fuel the cyclical bouts of HF regeneration and hair growth. By contrast, EpdSCs reside in the innermost (basal) layer of epidermis, where they generate an upward flux of differentiating cells that produces the skin’s barrier.

Upon injury, both Epd- and HFSCs near the wound site mobilize toward it, re-epithelializing the wound bed and restoring the barrier (Ito et al., 2005; Jensen et al., 2009; Levy et al., 2007; Tumber et al., 2004). Each lineage can also participate in cancer progression when its SCs acquire oncogenic HRAS mutations (Lapouge et al., 2011; White et al., 2011). At low levels, oncogenic HRAS drives the SCs to hyper-proliferative and benign tumorigenic states; as RAS/MAPK levels rise, malignant, invasive SCCs develop (Latil et al., 2017; Quintanilla et al., 1986; Rodriguez-Puebla et al., 1999) How SCs acquire the plasticity that allows them to exit homeostasis and participate in wound repair and malignant progression remains unknown.

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