Wnt Signaling and Injury Repair

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Wnt signaling is activated by wounding and participates in every subsequent stage of the healing process from the control of inflammation and programmed cell death, to the mobilization of stem cell reservoirs within the wound site. In this review we summarize recent data elucidating the roles that the Wnt pathway plays in the injury repair process. These data provide a foundation for potential Wnt-based therapeutic strategies aimed at stimulating tissue regeneration.

The Oxford English Dictionary's definition of repair is to "restore to good or proper condition by replacing or fixing parts." In contrast, regeneration is the process of complete renewal, characterized by a full restoration of form and function. Why do some organisms regenerate tissues after injury, while others do not? And is it possible to induce regeneration in cases where repair is the norm? In this article we discuss some of the recent discoveries that have been made by investigators seeking to understand these differences, and how they have used this information to develop therapeutic strategies aimed at stimulating a regenerative response to acute injury.

The "reproduction of lost parts" has long been a subject of intense curiosity. In the 18th century the Swiss naturalist Abraham Trembley demonstrated that when the Cnidarian polyp *Hydra* was divided into small fragments, each piece "grew again into perfect *hydrae*" (Trembley 1744). The Scottish biologist and mathematician D'Arcy Thompson was fascinated by these

early observations, and wrote that "the ability of an animal to regenerate lost parts [had] excited the interest of crowned heads... ambassadors, and state-couriers, who carried it through Europe" (Thompson 1884). Some years later the Vice President of the British Medical Association voiced a similar interest and wrote, "In these days of strife and stress, when fire and water play havoc with men's lives and limbs, limb regeneration... would be of inestimable value." Despite the fact that 238 years have elapsed since those initial observations, our curiosity about regeneration—and the possibility that we could harness this regenerative potential to aid in the healing of our own tissues—has not waned.

Our own regenerative capacities are remarkably limited. Early observers (Dinsmore 1992) who were interested in distinguishing "repair" from "regeneration" recognized that animals did not respond uniformly to an act of injury. In some cases, adult animals mount an injury response that results in the complete regeneration of the damaged tissue or organ; the appendage

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of the aquatic axolotl or the fins of a zebrafish are excellent examples (see Fig. 1) (Poss et al. 2000; Straube et al. 2004; Kawakami et al. 2006; Stewart et al. 2009; Satoh et al. 2010). In other cases, the same tissue or organ in a different species had a very limited regenerative response; for example, reptiles seem to lack this regenerative response, at least in their limbs (Galis et al. 2003), but most species retain the ability to regenerate their tails (McLean and Vickaryous 2011). In contrast, most mammalian tissues respond to injury by generating scar tissue (Harty et al. 2003), which is composed of granulation and fibrous tissues that are poorly organized and lack functionality.

One might interpret these observations to mean that an animal's regenerative capacity is species specific, but this is an oversimplification; some animals begin life with a robust regenerative response that wanes over time. Tadpoles, for instance, exhibit a regenerative capacity only up to metamorphosis; after this developmental event frogs cannot regenerate an amputated limb (Kawakami et al. 2006; Yokoyama et al. 2011). Avian embryos have some ability to regenerate a damaged retina but this potential is lost by the time they are hatchlings (Fischer and Reh 2000; Fischer and Reh 2001). Mammalian embryos also appear to possess an early regenerative ability that erodes by birth (Rinkevich et al. 2011). Why is there such variation in regenerative ability of animals, and between different stages of postnatal life? Such a question has obvious clinical importance, because if we understood the key features that distinguish hu-

man healing from that of our amphibian ancestors, then we could potentially "jump-start" a similar regenerative program (Kragl et al. 2009).

The observation that "simple animals" such as sponges and flatworms regenerate, whereas more complex organisms do not (Gurtner et al. 2008), is the basis for some theories that propose there is an association between regenerative capacity and tissue complexity (Sanchez Alvarado 2000). Many examples challenge this theory: the teleost, avian, and mammalian retinas exhibit very similar cellular architecture (Reh and Levine 1998). Yet fish can completely regenerate the neural retina (Cameron et al. 1999; Cameron 2000; Raymond et al. 2006), as can birds up to the hatchling stage (Coulombre and Coulombre 1965, 1970), but rodents and primates retain no such inherent regenerative capacity (Trophepe et al. 2000). Another theory proposes that regenerative abilities wane as the immune system matures (Mescher and Neff 2005, 2006). This theory is largely based on the observation that fetal wounds heal without scar formation, and this developmental period is associated with an immature immune system. A third theory posits that the loss of regenerative ability has evolved to curtail inappropriate cell division and malignant transformation (Gardiner 2005; Levesque et al. 2010). Perhaps most relevant to humans is the observation that across multiple species, regenerative capacity diminishes with age (reviewed in Silva and Conboy 2008; but see Eguchi et al. 2011 for conflicting data). The inference from these observations is that aging depletes a stem cell population

Figure 1. Regenerative capacity across species. The ability to regenerate tissues varies across species. Planarians can regenerate their entire body from a single fragment, fish and salamanders can regenerate their fins and limbs, while mammals have a relatively poor repair mechanism resulting in inadequate tissue replacement and scarring. A common goal of doctors and scientists is to develop biologic therapies to increase mammalian regenerative potential.

from which new body parts arise. But this interpretation has been repeatedly challenged, which leaves open an obvious question: if they are not from a reservoir, where do the cells come from that reform the missing or damaged tissues?

New data demonstrate that adult cells at the edges of the wound dedifferentiate to generate the new tissues (Straube et al. 2004; Kragl et al. 2009; Azevedo et al. 2011). This feature is not unique to mammals: The wound blastema of an axolotl is composed of tissue-specific progenitor cells that arise from the partial dedifferentiation of neurons, cartilage, and muscle (Kragl et al. 2009). What factors are responsible for stimulating this dedifferentiation of adult cells to a stemlike state or the recruitment of stem/progenitor cells into the regenerating tissue? Growing evidence implicates the Wnt pathway in this critical event.

In the following sections we present a summation of recent data supporting a model whereby the act of injury triggers the endogenous Wnt pathway, and that this pathway activity is essential for subsequent healing. Most data suggest that within a damaged tissue, the endogenous Wnt signal activates tissue-resident stem cells, and these cells contribute to the repair and/or regeneration of the damaged tissue. Augmenting this endogenous Wnt signal appears to enhance the healing response; consequently, a number of approaches are being tested that aim to activate Wnt signaling in a local, transient manner to stimulate tissue regeneration in humans.

WNT SIGNALING IS NECESSARY FOR TISSUE REGENERATION

Generally speaking, when Wnt signaling is reduced in an animal with robust regenerative capacities, their inherent regenerative abilities are impaired. For example, blocking Wnt signaling in planarians disrupts the polarity of the regenerate, resulting in inappropriate anatomical generation (i.e., the posterior half of the flatworm regenerates another posterior [tail] segment, and the anterior half generates another anterior [head] segment) (Gurley et al. 2008; Petersen and Reddien 2008, 2009; Yazawa et al.

2009). Likewise, blocking Wnt signaling after amputation of the dorsal fin in zebrafish impairs their normal fin regeneration (Kawakami et al. 2006). Inhibiting Wnt signaling in the eyes of animals with continually regenerating retinas results in an abrupt cessation in this regenerative ability (Kubo et al. 2003; Cho and Cepko 2006; Stephens et al. 2010; Ramachandran et al. 2011).

Which aspects of these regenerative responses are Wnt dependent? The early consensus seems to be that Wnt signaling blockade disrupts the recruitment of stem/progenitor cells to the injury site (Liu et al. 2007b; Das et al. 2008; Denayer et al. 2008; Stephens et al. 2010; Ramachandran et al. 2011) and adversely affects the proliferative phase of the healing process (Qyang et al. 2007; Stoick-Cooper et al. 2007). The formation of a blastema, the mass of multipotent cells at the tip of the wounded limb (Bryant et al. 2002), depends upon recruitment and proliferation (Agata et al. 2007). Consequently, perturbations in Wnt signaling in these regenerating animals manifest as disruptions in the aggregation of morphologically undifferentiated cells that comprise the blastema.

In mammalian organs and tissues with limited regenerative capacity, Wnt signaling is still necessary for the repair process. For example, when Wnt signaling is blocked after skeletal fracture, the result is a nonunion of the injured bone (Chen et al. 2007; Kim et al. 2007; Leucht et al. 2008a). Inhibition of Wnt signaling during skin wounding prevents formation of epithelial appendages including hair and sweat glands, which results in prominent scarring of the epidermis (Ito et al. 2007). Myocardial infarctions in mammals produce a region of scar tissue surrounding the occluded vessels and if Wnt signaling is repressed, the scarring worsens and the result is myocardial rupture (Chen et al. 2004).

If Wnt signaling is required for tissue regeneration, can elevating Wnt signaling in animals with limited regenerative capacity improve the healing response? Current data support this hypothesis. For example, when the limb of a post-metamorphic frog is amputated, the result is a “spike,” an outgrowth that lacks any discernible digits. This spike can be converted into a fully functional limb, complete with all appendages,

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provided that Wnt signaling is elevated at the time of amputation (Kawakami et al. 2006) (although, see Yokoyama et al. 2011 for a differing opinion). Mammalian skin wounds typically heal by scarring; however, elevating Wnt signaling within the wound site leads to the growth of new hair follicles, a hallmark of a fully functional epidermis (Ito et al. 2007).

Even in diseases that are characterized by tissue destruction, elevating Wnt signaling can induce a repair of sorts. For example, multiple myeloma is a cancer of the plasma cells in the bone marrow that is distinguished by severe osteolytic lesions (Sezer 2005). This osteolysis has been linked to elevated levels of Dkk1 in the bone marrow cavity (Tian et al. 2003; Kaiser et al. 2008). Phase I/II clinical trials are now under way to test the efficacy of enhancing Wnt signaling via antibody-mediated repression of Dkk1 as a means to stimulate new bone formation in multiple myeloma patients (Yaccoby et al. 2007; Fulciniti et al. 2009). Likewise, some inflammatory bowel diseases are characterized by reduced Wnt pathway activity (Wehkamp et al. 2007) and reduced turnover of stem cells in the intestinal crypt (Sato et al. 2009). In these types of debilitating chronic injury states, transiently elevating Wnt signaling may be beneficial (reviewed in Anderson and Wong 2010). Indeed, such a Wnt-based therapeutic approach has been attempted. Oral mucositis is a frequent occurrence following chemotherapy, and is characterized by inflammation and ulceration of the mucosal lining of the digestive tract. Investigators demonstrated that they could stimulate regeneration of the mucous membranes in mice using systemic administration of the Wnt agonist, R-spondin (Zhao et al. 2009a).

Collectively, these data demonstrate that endogenous Wnt signaling is a prerequisite for tissue repair, but there are obvious caveats. Most experimental methods used to study Wnt signaling in tissue healing rely on techniques that, in general, produce unrestrained Wnt pathway activation. A well-documented effect of constitutively active Wnt signaling, however, is cancer (Chan et al. 1999; de Lau et al. 2007; Vermeulen et al. 2010), so experimental methods to test the role of Wnt signaling in healing must take this

into account. Likewise, increasing Wnt signaling, via genetic deletion of negative regulators such as Ror2 (Brunetti-Pierri et al. 2008) and Axin2 (Liu et al. 2007a; Minear et al. 2010), or mutations in Wnt coreceptors such as Lrp6 (Boyden et al. 2002) or Wnt ligands themselves (Liang et al. 2003), have their own adverse sequelae. Clearly, what is required is a means to activate the pathway in a local, transient manner with the goal of restoring the endogenous Wnt response that is necessary for normal healing. But when should the Wnt pathway be activated? And what, precisely, does Wnt signaling contribute to the injury repair response? The answers to these questions will undoubtedly inform strategies that aim to take advantage of the Wnt pathway for regenerative medicine therapies, and thus we review recent data addressing these questions in the following paragraphs.

WNT SIGNALING AT THE INITIAL STAGE OF THE INJURY RESPONSE

When the body is injured, a cascade of events is set into motion that have as their most fundamental objective the cessation of bleeding, followed by an attempt to wall off the injured tissues from the rest of the body to maintain homeostasis. This vascular response occurs within minutes of tissue damage, and is largely due to the hypoxic condition that develops in tissues deprived of a vascular supply.

The activation of β -catenin-dependent Wnt signaling appears to be one of the initial molecular responses to injury. This activation is typically rapid and spatially restricted, in most cases to the site of damage. For example, severing a planarian in half leads to the rapid up-regulation in Wnt gene expression specifically at the cut site (Petersen and Reddien 2009). Wnt signaling is also initiated by bone fracture (Chen et al. 2007; Kim et al. 2007; Leucht et al. 2008a), by exposure to ionizing radiation (Gurung et al. 2009), by inhalation injury to the lung (Villar et al. 2011; also reviewed in Beers and Morrissey 2011), skin wounding, laser damage to the retina, myocardial infarction, and stroke (see Fig. 2, showing unpublished results from multiple laboratories).

Figure 2. Wnt signaling is activated in response to injury. Damage in most tissues up-regulates Wnt signaling transiently at the injury site. While too much Wnt signaling has been shown to be deleterious, a number of studies have shown that the exogenous addition of Wnt signaling stimulates healing in a number of different injuries, including bone fractures, retinal damage, skin wounding, and myocardial infarction. (Wnt response seen here in blue, by X-gal staining of murine *Axin^{LacZ/+}* tissue.) (Heart images are thanks to Professor Joseph Wu.)

What features of injury lead to activation of the endogenous Wnt pathway? One intriguing possibility is oxygen tension: Embryonic stem cells—but not differentiated cells—respond to hypoxic conditions by up-regulating the expression of hypoxia-inducible factor (HIF)-1 α and in turn, HIF1 α regulates expression of the Wnt target genes *Lef1* and *Tcf1* (Mazumdar et al. 2010). If this in vitro observation is validated in vivo, then changes in oxygen availability and, by extension, HIF-1 α activity, may be the direct trigger between injury and activation of the Wnt pathway.

INFLAMMATION AND WNT SIGNALING

Within minutes of tissue injury, platelets aggregate at a wound site to form a clot that both protects surrounding tissues from the invasion of microorganisms, and acts as a reservoir for growth factors that will eventually serve to recruit cells to repair the damage (reviewed in Midwood et al. 2004; Nurden et al. 2008). Although the role of Wnt signaling in platelet regulation during wound healing in vivo is unclear, one study suggests that β -catenin-dependent Wnt signaling inhibits platelet aggregation, at least in vitro (Steele et al. 2009).

Within hours of injury, the inflammatory response ensues: Neutrophils, monocytes, and lymphocytes invade the wound bed in an attempt to phagocytose cell debris and release growth factors and cytokines (Newton et al. 2004; Martin and Leibovich 2005). The inflammatory response is crucial for fighting infection but a state of chronic inflammation is largely considered to be detrimental, both to healing and to the program of regeneration. Some speculate that the mammalian immune system has evolved in such a way as to optimize tissue repair through fibrosis but that these modifications have been detrimental to the program of tissue regeneration (Mescher and Neff 2005). However, direct demonstration of a causal relationship between the inflammatory response and tissue regeneration is lacking. By selectively depleting cells of the neutrophil lineage from a wound site, investigators demonstrated that inflammation can retard wound closure (Dovi et al. 2003; Martin and Leibovich 2005), but how this affects tissue regeneration remains unknown.

The role(s) of Wnt signaling in the inflammatory response is poorly understood. β -catenin-independent Wnt signaling may be a proinflammatory stimulus, based on the observation that *Wnt5a* expression is increased in the sera of

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patients suffering from severe sepsis (Pereira et al. 2009). β -Catenin-independent Wnt signaling has also been implicated in a number of chronic inflammatory diseases such as rheumatoid arthritis (Sen et al. 2000) and atherosclerosis (Polzer et al. 2008), but in these cases a causal link between Wnt function and etiology of the inflammatory disease has not been established.

β -Catenin-dependent Wnt signaling, on the other hand, may inhibit or restrict the inflammatory response, based on the observation that inhibitors of the pathway increase the expression of some genes associated with inflammation (Kim et al. 2010). A more direct link has come with the demonstration that by elevating Wnt signaling through inhibition of Dkk1, the bone-resorbing phenotype observed in a mouse model of rheumatoid arthritis could be replaced with the bone-forming pattern of osteoarthritis (Diarra et al. 2007; reviewed in Baker-LePain et al. 2011). The theory that a reduction in Wnt signaling causes inflammatory bone loss is further supported by the observation that osteolytic lesions in multiple myeloma are associated with unrestricted Dkk1 activity (Tian et al. 2003). But it must be emphasized that these effects of Wnt signaling are largely attributed to a pro-osteogenic influence and not because Wnt signaling directly impacts inflammatory mediators. For example, in the condition of rheumatoid arthritis, tumor necrosis factor (TNF) contributes to the disease pathology because the cytokine increases the activity of bone-resorbing osteoclasts; Wnt signals counter this effect by stimulating osteoblast activity.

WNT SIGNALING AND THE PROLIFERATIVE PHASE OF WOUND REPAIR

Within days or months of an injury, the proliferative phase develops, and it is here that the difference between repair and regeneration becomes most obvious. In the repair program, granulation tissue accumulates at the wound site, which is composed of new blood vessels and highly proliferative fibroblasts that produce copious amounts of fibronectin, collagen type III, glycosaminoglycans, elastin, glycoprotein, proteoglycans and hyaluronan (Buchanan

et al. 2009). This matrix appears to support cell migration but it is transient; gradually, a collagen type III-rich matrix that provides tensile strength to the wound site replaces the granulation tissue. In the regeneration program, the hyaluronan content of the extracellular matrix is much higher, and investigators speculate that this may curtail or reduce that amount of collagen deposited at the wound site by overproliferative fibroblasts (Carre et al. 2010). In support of this theory, investigators showed that hyaluronan removal results in fibrotic scarring (West et al. 1997), and that Wnt3a induces hyaluronan synthesis (Larson et al. 2010).

In the intestine, Wnt signaling maintains crypt architecture (reviewed in Clevers 2006; Sansom et al. 2007; van der Flier and Clevers 2008) and does so by being a positive stimulus for proliferation. Investigators demonstrated that the Wnt inhibitor Dkk1 is induced by inflammatory cytokines during colitis. Dkk1 causes further tissue damage by stimulating epithelial cell apoptosis. Blocking Dkk1 function results in elevated Wnt signaling and the induction of cell proliferation, which promotes wound repair after colitis (Koch et al. 2011). The experimental approach in this particular study, however, resulted in abolition of Dkk1 function and therefore unrestricted Wnt signaling, which had its own set of side effects, namely, hyperproliferation of the epithelial cells lining the crypt (Koch et al. 2011). These and other studies in skin wound healing (Ito et al. 2007) and bone formation (French et al. 2004; Friedman et al. 2009) and repair (Kim et al. 2007) emphasize that the proliferative effects of β -catenin-dependent Wnt signaling must be transient and localized to be beneficial in the wound repair/regeneration process.

In the final stages of wound repair, extensive extracellular matrix remodeling occurs. In repair, the granulation tissue is converted to mature scar tissue through collagen synthesis and catabolism (Chang et al. 2004). Type III collagen is gradually degraded and is replaced by the stronger type I collagen. Proapoptotic signals at the injury site can regulate collagen degradation both by decreasing fibroblast numbers and by initiation of collagenase activity (Rai et al.

2005). These collagen fibers are rearranged, cross-linked, and aligned providing increased strength to the wound. Over time, this densely packed collagen develops into an inelastic white collagen scar. Regeneration, on the other hand, has no such fibrous tissue. A schematic of the stages of wound repair is shown in Figure 3.

CHRONIC INJURY, CANCER, AND WNT SIGNALING

Multiple lines of evidence demonstrate that overactivation of the Wnt pathway causes hyperproliferation and cancer (reviewed in Barker

and Clevers 2006). The majority of these cancers are due to loss of function mutations in Wnt pathway inhibitors. There are also clear examples of an intimate relationship between chronic injury and cancer initiation (see Fig. 4). For example, smoking inflicts chronic injury of the trachea and lung tissue, resulting in lung cancer (Kersting et al. 2000), extensive sun exposure leads to prolonged inflammation of the dermis and can result in melanomas and other skin cancers (El Ghissassi et al. 2009), and chronic alcohol consumption causes inflammation and death of hepatocytes, which can result in liver cancer (McKillop and Schrum 2005).

Figure 3. Wnt signaling drives tissue repair. In both repair and regeneration, wound healing is characterized by three main phases. During the inflammatory phase there is an influx of inflammatory cells and local Wnt signaling begins to increase. During the proliferative phase a scab (eschar) is formed and the wound is reepithelialized. This phase includes an increased local Wnt response, extracellular matrix deposition, angiogenesis, and the recruitment and proliferation of multiple cell types including stem cells, keratinocytes, and fibroblasts. The third phase, the maturation and remodeling phase, is characterized by extensive extracellular matrix remodeling. Whereas repair leads to scarring, or functionally inadequate tissue, increased Wnt signaling during regeneration leads to a reduced inflammatory response, increased angiogenesis, increased cellular proliferation and recruitment, as well as differences in matrix composition, leading to the complete reconstruction of the original tissue architecture. (Increase in blue color represents an increase in Wnt signaling.)

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Figure 4. Does chronic injury lead to prolonged Wnt signaling and cancer? Injury results in a local increase in Wnt signaling and chronic injury leads to cancer. Many cancers also have up-regulated Wnt signaling. The Wnt pathway is best known to promote proliferation; an intriguing possibility is that chronic injury may induce a prolonged Wnt response leading to uncontrolled cell proliferation and cancer. In the lungs, cigarette smokers inflict chronic injury to the trachea and lung tissue, which may result in lung cancer. Relating to the skin, prolonged UV exposure leads to chronic inflammation of the dermis, which may result in skin cancer. In the liver, chronic alcohol consumption subjects the tissue to constant damage, which may lead to liver cancer.

Abundant data demonstrate that injury locally activates Wnt signaling (see previous paragraphs), but does chronic injury cause inappropriately prolonged Wnt signaling, thus heightening the risk of cell transformation at the site of injury? Growing data support this hypothesis: Wnt1 is overexpressed in nonsmall cell lung carcinoma (He et al. 2004) and some melanoma cell lines exhibit abnormally high levels of β -catenin (Rubinfeld et al. 1997). More recently, investigators demonstrated that melanoma cells have evolved a mechanism to activate β -catenin-dependent signaling that does not require high levels of Wnt ligands (Sinnberg et al. 2010; reviewed in Vaid et al. 2011). Thus, the connection between protracted, repeated injury, persistent Wnt pathway activation, and tumorigenesis is compelling, and

represents a novel hypothesis to explain the molecular etiologies of injury-related cancers.

HARNESSING THE WNT PATHWAY FOR THERAPEUTIC APPLICATIONS IN INJURY REPAIR

There is significant interest in finding ways in which the Wnt pathway can be modulated for therapeutic purposes (see Fig. 5). A number of small molecules have been identified that can activate or inhibit the pathway but thus far, they all depend upon Wnt ligands to exert their effects (reviewed in Leucht et al. 2008b). Recombinant proteins such as the Wnt agonist R-spondin (Kazanskaya et al. 2004; Kim et al. 2008) have been used to treat oral mucositis (Zhao et al. 2009a), and recombinant Wnt3a

Figure 5. Harnessing Wnt signaling for therapeutic applications in injury repair. There are many biological ways to activate or repress the Wnt signaling pathway; these may be therapeutic options for increasing a healing response or reducing uncontrolled proliferation. The use of small molecules, microRNAs, genetically modified cells, as well as ligands and inhibitors, are all potential future therapeutics for both activating and repressing the Wnt signaling pathway.

protein has been used to transiently elevate Wnt signaling in bone injury sites and in cases of implant osseointegration (Zhao et al. 2009b; Minear et al. 2010; Popelut et al. 2010). In these cases, the hydrophobic Wnt protein has been packaged into a lipid vesicle that maintains its activity in vivo (Morrell et al. 2008).

Anti-Dkk1 antibodies have been employed to treat the osteolytic lesions associated with multiple myeloma (Fulciniti et al. 2009), and antisclerostin antibodies are in phase I trials for the treatment of rheumatoid arthritis (Choi et al. 2009). Although microRNAs and small interfering RNAs have been identified that effectively block activity of Wnt pathway components (Korpai et al. 2008; Thatcher et al. 2008; Hashimi et al. 2009), it is unclear whether they have the ability to regulate Wnt signaling at sites of injury. Such an approach is likely to be challenging since a single miRNA can have multiple mRNA targets, each target can be regulated by several mi-

RNAs, and the effects of a specific miRNA are variable depending on the cell context.

CONCLUDING REMARKS

Converting tissue repair to tissue regeneration remains a lofty goal, but growing evidence suggests it is a realistic objective. We now know that almost every adult tissue harbors stem cells with potential to regenerate damaged or diseased tissues. But there are problems: adult stem cells are usually found in low abundance, and their response to stress and aging typically diminishes their ability to self-renew and proliferate. Endogenous Wnt signaling regulates stem cell recruitment and differentiation during the wound repair process, which suggests that modulation of Wnt signaling can positively influence the injury repair process. Strict attention will have to be paid to controlling Wnt signaling in a spatial and temporal manner in order to avoid

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the well-documented untoward effects of unrestrained Wnt pathway activity.

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