Tissue Regeneration: Past, Present and Future

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Regeneration research established its roots in the eighteenth century when it firmly debunked the established theories of reproduction by disproving pre-formation. It was then that the classical models (invertebrates and salamanders) exemplified their astonishing capabilities for regenerating body parts. Since that time, regeneration has captured the fascination of scientists and has been often portrayed as one of the most important scientific questions to be answered.

In our time, regeneration research has come into the spotlight through recent molecular exploitation of the classical models as well as through a better (albeit partial) understanding of the potential of somatic and embryonic stem cells. However, no serious research effort has been exerted at the interface between these two areas, which, rather than being disparate and exclusive, should be viewed as complementary. It is well known that newts, for example, regenerate amputated limbs or removed lenses and retina through transdifferentiation of terminally differentiated somatic cells at the site of injury. Stem cells, on the other hand, are involved in repair of damaged tissues and do not have to be local—they can be recruited from sites distal to the site of injury and can be stimulated to differentiate by specific damage-indicating signals. Maintenance of their undifferentiated state is controlled by several factors. Different stem cells also possess a molecular signature that characterizes their "stemness" state (i.e., true characteristics of stem cells). How is the biology of stem cells related to the biology of dedifferentiating newt cells? All these issues bring up the next question: How will regeneration research make an impact in the biomedical field? There are two major challenges of regeneration research. One is to gain understanding of the extraordinary biological phenomenon and explain its relationship to development and evolution. Because a trait should be beneficial to the organism, regeneration (for example, in newts) should make sense in terms of evolutionary success. Nevertheless, at this point, it is quite difficult to answer why regenerating a lens is advantageous to a newt and not to a primate. Therefore, the biology of the newt might be unique for regeneration. And because of this, gene regulation could be governed by unsuspected mechanisms. Such mechanisms could also be shared by stem cells as well, under the umbrella of the stemness mentioned above. The second challenge is to use this knowledge to find cures for replacing damaged tissues. The need for organs to be transplanted is great but the supplies are limited. Contrary to the popularization of the issue, however, answering the questions of one challenge does not necessarily mean that the other will be achieved. In other words, even if we understand how the newt regenerates a limb, it does not necessarily follow that we would accomplish the same feat in humans. The reason might have to do with unique animal biology or other evolutionary constraints. It would be of great benefit if salamanders could teach us how to grow lost legs and repair damaged brains, but how realistic is such an expectation? If, in the end, we do face such a deterrent, what is the future of regeneration? The solution might be provided from another research front. Recent advances in bioengineering are quite promising for building-up tissues. Scaffolds, local cells, and growth factors have been utilized to engineer tissues. Research on biomaterials—especially for 3-D scaffolds—is important because factors such as matrix stiffness can direct stem cell differentiation. Our research explores all these issues in a combined effort to better understand and apply regeneration.