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Abstract

Organ and limb regeneration might seem like something out of science fiction, but research has been ongoing since the late 1960s and has greatly increased at the turn of the century. It is an understatement to say that this has the potential to be life changing. The need for donor transplant organs and transplant waiting lists can become obsolete and the use of immunosuppressants post-transplant will become unnecessary (leading to higher survival rates). Should this happen, trauma patients will be able to achieve complete recoveries and the reign of some congenital disorders will come to an end. Nature has provided several opportunities for us to study this subject. Many species have a natural ability to regenerate complete organs. Human fetuses display a tremendous power of regeneration and healing in utero. The struggle has been in determining how and why this ability disappears after birth as well as applying the lessons we have learned from other species to humans. (However, great progress has been made and this paper will discuss where science is holding in terms of being able to give a human the ability to regenerate complete organs and limbs.) This paper will discuss whether science has been able to determine which lessons to learn from nature and how and when to apply it.

Introduction

In 2008, nearly 2 million amputees have been reported in the United States and its prevalence is estimated to escalate more than 3-fold by 2050 (Ziegler-Graham, et al., 2008). Although great strides have been made in treatments for amputees which have in turn greatly increased their ability to lead productive lives, there are many side effects and frequent compromises that affect the quality of life (i.e. the adverse effects of long-term immunosuppression) need to be accepted. In addition, current therapeutic approaches, such as allogeneic hand transplantation, suffer from a limited donor supply (Schneeberger, et al., 2007). Besides for injuries and congenital diseases, regenerative medicine therapies have the potential to allow us the ability to treat (or even replace) failing organs which have begun to decline due to age (Heidary Rouchi, Mahdavi-Mazdeh, 2015; Ranjeet Singh, 2016). This will allow for a great increase the general quality of life, especially for the elderly. Regenerative medicine has the potential to provide treatment for a tremendous variety of currently intractable diseases and ailments (Upadhyay, 2015).

Methods

Data was collected using Google and PubMed databases through Touro College's online library. Among the key-phrases used were "regeneration", "limb regeneration", "human regeneration", and "regenerative medicine."

Discussion

To begin the discussion of regeneration we must first gain a clear understanding of the conditions and processes that are required for it to occur. There are a few species that have a natural ability to regenerate organs and limbs. All known livings things can be classified into three groups concerning their natural ability to regenerate. This paper will refer to the three groups as "complete", "partial", and "minimal". "Complete" refers to a lifelong, absolute ability to regenerate complete organs and limbs. Examples include urodeles such as newts and axolotls such as salamanders (Bensoussan-Trigano, et al., 2011; Dinsmore, 1996; Brockes, Kumar, 2002; Roy, Lévesque, 2006). "Partial" refers to an absolute ability to regenerate but only for a portion of the lifespan, after which the capacity is lost. For example, anurans such as frogs and toads can completely regenerate a limb in the larval stage, however, once passed metamorphosis they lose this ability (Satoh, et al., 2005; Suzuki, et al., 2006). "Minimal" refers to a very limited capacity for regeneration (only very simple organs and/or simple portions of complex organs) and only for a small portion of the lifespan. Neonatal mammals for example, have been shown to be able to regenerate the tips of digits, however, this ability fades with aging (Sánchez Alvarado, Tsonis, 2006; Farah, et al., 2016).

Differences

Wound healing is a necessary component of regeneration and is comprised of four stages (a) hemostasis (blood clotting), (b) inflammation, (c) proliferation (growth of new tissue including the formation of wound epidermis (WE)), and (d) maturation (remodeling) (Fernando, et al., 2011; Simkin, et al., 2013; Yokoyama, 2008). Wound healing occurs in all groups, regardless of their ability to regenerate (Raz, Mahabaleshwar, 2009). However, there are important variances within the exact mechanisms for each of the groups (Borgens, 1982; Han, et al., 2008; Takeo, et al., 2013). Variances include the duration of wound closure (Mu, et al., 2013; Stocum, 2011), inflammatory response (Ferguson, et al., 1996; Wulff, et al., 2012), and wound maturation (remodeling) (Bellayr, et al., 2009; Ravanti, Kähäri, 2000; Xue, et al., 2006). Understanding these variances is essential for developing regenerative capacity in humans (Mu, et al., 2013). The differences will be highlighted here, for a more thorough review of the mechanism for limb regeneration refer to "New Insight into Functional Limb Regeneration: A to Z Approaches" (Taghiyar, et al., 2018)

Wound Closure

Unlike adult anurans and mammals (postnatal) who form scar tissue during wound healing, urodeles, embryonic and fetal anurans, and neonatal mammals do not (Dang, et al., 2003). One difference is the length of time it takes for wound closure in each of these groups. In adult mammals, epidermal closure takes between 8- and 12-days post amputation (DPA) (Reginelli, et al., 1995; Simkin, et al., 2013). Embryonic mammals, however, take much shorter time. A study found it takes only up to 24 hours for an embryonic mouse (McCluskey, Martin, 1995). In addition, urodeles take only between 10 and 24 hours (Campbell, Crews, 2007; Murawala, et al., 2012) and a study conducted on early post-metamorphic anurans found the wound closure time to be between 2 and 3 days (Goode, 1967). Last, a study on embryonic tadpoles (which are anurans) found wound closure took only 30 mins though the paper does admit that this rate seems "extremely high" (Yoshii, et al., 2005). It logically follows that scar tissue formation is related that the length of time required for complete wound closure (Manuel, Gawronska-Kozak, 2006; Wilgus, 2007). Though it seems the differences between those with scar formation and those without must manifest sometime after 24 hours, this is not the case. The first 24 hours of each of the groups are not the same. In fact, in (adult) mammals, it can take more than 24 hours for the first migration of epithelia to begin to cover the wound. There seems to be a fundamental difference in the wound healing process that must be explored..

Immune System

One such fundamental difference seems to be the immune system. Urodeles have a weak immune system compared to anurans and mammals (G. Chen, Robert, 2011; Kaufman, et al., 1995) who seem to share the same immune system in terms of complexity, specificity, and memory (du Pasquier, et al., 1989; Mescher, Neff, 2005). This isn't the only place where anurans and mammals are grouped together. Interestingly, the changes that occur in mammals as they mature and shift from fetal scar-free repair to adult scar-based repair have a close resemblance to the changes that occur in anurans as they begin metamorphosize and lose their regenerative ability and in both cases immune signaling has been identified as a key regulator. In mammals specifically, scar-free healing is associated with an immature immune system. (Kishi, et al., 2012; Wilgus, 2007). Also, note that although most of what we know about urodeles immunity has been obtained from studies on axolotls specifically, it appears it can be inferred to the many different species and genre of salamanders (Cohen, 1971).

Past research indicates that there is a correlation between the level of maturity of an immune system and the regenerative capacity. As an anuran undergoes metamorphosis (a developmental period referred to as "refractory period"), we find an inverse relationship between the maturation of their immune system and the loss of scarless healing (Bertolotti, et al., 2013; Godwin, Brockes, 2006; Mescher, Neff, 2005). In fact, the suppression of the more potent immune response that develops during the refractory period restores a metamorphosizing anuran's regenerative ability (Fukazawa, et al., 2009). This is backed up by another study that found that the decrease in regenerative capacity that an anuran experiences as it matures is negatively correlated with the intensity of the inflammatory response as well as structural modifications in the thymus (Franchini, Bertolotti, 2012).

Comparison of Systems

The immune system of adult anurans and mammals is intricate with a wide range of adaptive immune responses in addition to a complete innate immune response. By comparison, urodeles are considered immunodeficient relative to adult anurans and mammals though they have a strong innate immune system (G. Chen, Robert, 2011). This is because, despite their reasonable B-cell and sizable T-cell reserves, their humoral response is extremely slow (60 days), not able to facilitate anamnestic responses, and only has one unique IgM class (Kaufman, et al., 1995; Tournefier, et al., 1998). In addition, immunization with soluble antigens gives negative results and its B cells are not triggered by T-helper cells; in fact, thymectomy, X-ray irradiation or corticosteroid treatment has shown to improve the humoral response (Charlemagne, 1979; 1981; Tournefier, 1982).

A urodeles cytotoxic immune response is very slow as well (21 days) and shows weak mixed lymphocyte reactions (MLRs) (Kaufman, et al., 1990; Koniski, Cohen, 1992) causing there to be no acute xenograft rejection reactions. However, since they have reasonable B-cell and sizable T-cell reserves they have a large diversity of B and T cell antigen receptors which, over time, causes rejection to ultimately occur. Therefore, xenograft rejection appears to be dependent on the thymus (Tournefier, et al., 1998). Due to the weak adaptive immune response of urodeles they are extremely susceptible to viral infections relative to anurans. Although they display a complex immune response, they fail to generate adequate T cell proliferation in the spleen early on. By comparison, anurans are able to generate adequate T cell proliferation in the spleen early on and therefore are capable to clear viral infections (Cotter, et al., 2008).

There are further differences, specifically in terms of innate vs. adaptive immunities (Godwin, Rosenthal, 2014) that are beyond the scope of this paper. However, clearly there are differences that seem to correlate with the ability for regeneration. The specific aspect(s) of the immune system that is/are responsible is still not known, but it appears that the more sophisticated the immune system is, the less of a regenerative ability there is. Perhaps this is the way species have evolved; prioritizing survival (by prevention of infection) over function and aesthetics of damaged organs and limbs. However, now that we have antibiotics, perhaps both can be achieved.

Wound Maturation

Analogous to the cytoskeleton in cells the extracellular matrix (ECM) allows for individual cells to come together and create tissues and eventually organs by providing a non-cellular structural platform upon which the cells adhere to. It is made up of macromolecular network composed of collagens, proteoglycans/glycosaminoglycans, elastin, fibronectin, laminins, and several other glycoproteins (Bonnans, et al., 2014; Michel, et al., 2010; Theocharis, et al., 2016). For organ or limb regeneration to occur, the proper ECM form must be created for the cells to have a place to go. In addition, the interaction between the cells and the ECM allows for the control of growth by providing negative feedback when a sufficient number of cells have been produced preventing an overgrowth.

Matrix Metalloproteinase (MMP)

During regeneration, for the proper structure to be formed the use of matrix metalloproteinases (MMPs) are employed. The main function of these molecules is to degrade the matrix strategically and help sculp the proper structure needed. There are other functions that have been discovered but they are beyond the scope of this paper. To keep things in control, tissue inhibitors of metalloproteinases (TIMPs) keep the protease activity of MMPs in check and therefore are the regulators of wound closure, tissue regeneration and scar formation (Mu, et al., 2013).

In adult mammals a severe inflammatory response and high fibroblast activity results in collagen fiber accumulation between the epidermal layer and the transected bone (Satoh, et al., 2012; Seifert, et al., 2012). The collagen deposition hinders a reciprocal interaction between the surface layer and most underlying mesenchymal tissues preventing normal skin restoration and causing scar formation to occur (Satoh, et al., 2008). The discrepancy between scar formation and epimorphic regeneration is most probably attributed to the histolysis phase of regeneration in which MMPs are absent for ECM remodeling (W. Chen, et al., 2007).

In urodeles, pre-morphologic anurans, and fetal mammals, higher ratios of MMPs/TIMP have been observed relative to those who do not have a regenerative capacity (Parks, 1999; Ravanti, Kähäri, 2000). Studies have shown that MMP1 specifically has a beneficial impact on muscle healing (note: these studies were completed on those that do not have a natural regenerative capacity) (Bedair, et al., 2007; X. Chen, Li, 2009; Kaar, et al., 2008; Wang, et al., 2009). In fetal mice, who are not able to regenerate complete limbs, introduction of MMP1 has been able to cause complete regeneration (Muneoka, et al., 2008). There have been many additional benefits observed when the use of exogenous MMP1 has been employed. Building on the results of the study by Chen et. al. (2007) stated above, results of a study from 2013 showed that in adult mice who underwent MMP1 treatment achieve an increase in the formation of capillary blood vessels, peripheral nerve fibers and neuromuscular junctions, as well as a decrease in the formation of fibrotic scar tissues in the amputated digits. However, the healing of skeletal tissue and digit elongation was not significantly improved (Mu, et al., 2013). A possible solution may be stem cells which are able to form the segmented pattern of bone and cartilage crucial needed for regeneration (more on this later on) (Masaki, Ide, 2007).

Additional Hypotheses

Land vs. Sea

An anuran loses its regenerative ability as it transitions from living in the water to living, at least partially, on land. As noted above the changes to the immune system of anurans as they metamorphosize and transition from water to land leave it with a much more powerful weapon, which makes sense as terrestrial conditions require a more effective immune system (Alibardi, 2018). However, a study on Xenopus laevis (anuran) embryos found that the rate of wound closure tends to decrease as the osmotic pressure approaches isotonicity (Yoshii, et al., 2005). The authors suggest that perhaps the extremely rapid rate of wound closure is a result of the stimulation of the osmotic pressure regulation system, something which amniote embryos do not require and therefore why they have a much slower rate of wound closure. This begs the question; why do urodeles have an increased wound closure rate if they are terrestrial organisms? While it may be true that osmotic pressure can affect an organism's ability to regenerate, it is unlikely for urodeles and pre-metamorphic anurans to have developed two completely distinct methods of regeneration, especially since anurans and

urodeles are part of the monophyletic Lissamphibians. In addition, of the three orders included, anurans and urodeles are more closely related to each other than to the third order (the legless caecilians) (Elinson, del Pino, 2012). More likely, once an organism has the ability to regenerate, the increased wound closure rate due to osmotic pressure helps speed up the process. However, research into this is unnecessary since we are looking for a way to replicate the mechanism of regeneration in humans and since humans do not have an osmotic pressure regulation system, increasing osmotic pressure to induce regeneration would be futile. Though, perhaps once we are able to regenerate maybe we can use the principles of osmotic pressure to help speed up the process without compromising on the regenerative ability.

Intrinsic and Extrinsic Cellular Properties

If there are fundamental cellular differences between those with the ability to regenerate and those without, then the potential for humans to achieve this capacity will be considerably more challenging. In that case it would require edits to the genetic code which we are a long way from being able to do at this point. Fortunately, although some evidence indicates that regenerative capacity stems from intrinsic cellular properties, it is not much. For example, transplantation of limb blastemas from post-metamorphic (regeneration incompetent) to larval (regeneration competent) stages failed to regenerate despite the conducive host environment. This seems to indicate that there may be an intrinsic property of those post-metamorphic cells that prevents regeneration from occurring (Sessions, Bryant, 1988). However, this conclusion is only theoretical and evidence for manipulation of extrinsic (specifically immunological) properties have yielded some interesting results in mammals (Leavitt, et al., 2016; Satish, Kathju, 2010). Genetic deletion of the anti-inflammatory cytokine IL-10 induces scar tissue formation in fetal mice (recall embryonic mammals heal scarlessly) (Liechty, et al., 2000). Though, in all fairness, these results were achieved by genetic manipulation. In order to be certain that there is no intrinsic cellular property that is responsible for regeneration, this study must be performed without any manipulation of any intrinsic cellular properties (i.e. no genetic deletion). For all we know, the deletion IL-10 caused some other effect, and which may very well be the actual reason for the results that were achieved.

Treatment Proposals

With the above in mind we will now explore some of the therapeutic approaches that been hypothesized to enable humans to be able to regenerate organs and limbs. These hypotheses include modulating the host environment, manipulation of the host immune system, and gene manipulation. However, we must keep in mind that the best possible solution might be to combine multiple approaches simultaneously. We will try to determine which discoveries discussed above form the basis for the proposed treatments to build upon.

Cell-Based Approaches

Many of the concepts discussed above describe differences that develop because species are inherently different down to the cellular level. This is true for all living things on an individual level as well. For example, the liver contains two types of epithelial cells named hepatocytes and cholangiocytes. However, both those cells originate from a single cell type called hepatoblasts (which are fetal liver stem/progenitor cells) during development (Oertel, et al., 2003; Tanimizu, et al., 2003). To overcome the lack of regenerative capacity of differentiated tissues, many have hypothesized harnessing the power of stem cells. Since stem cells are inherently able to develop into multiple cell types, we can theoretically achieve an environment that is similar to a fetus (recall that mammal fetuses do possess an ability to regenerate to some extent). However, due to ethical concerns related to the use of embryonic stem (ES) cells as well as the desire to move away from the use of immunosuppressant drugs commonly used nowadays post allogeneic or even xenogeneic transplantations due to rejection, many have turned to the use of the patients own cells and then "reprogramming" them into a stem cell that behaves like an embryonic one. ES cells are pluripotent, meaning they can form tissues from all three primary germ layers (ectoderm, endoderm, and mesoderm). Somatic cells that have been reprogrammed to behave like ES cells are called induced pluripotent (iPS) cells. This is achieved through a number of techniques which artificially turn on expression of specific pluripotency genes (Hackett, Fortier, 2011). Last year, a study to trace the origin of adult intestinal stem cells provided a direct link between the observed plasticity and cellular reprogramming of differentiating cells in adult tissues following damage (Tetteh, et al., 2016; van Es, et al., 2012; Buczacki, et al., 2013; Yui, et al., 2018; Nusse, et al., 2018). This indicates that stem-cell identity is an induced rather than a hard-wired property (Guiu, et al., 2019).

Amongst the various candidates for reprogramming, mesenchymal stem (MS) cells are of central importance for several reasons. MS cells are found in a majority of adult tissues including, bone marrow, adipose, cartilage, and dental pulp (Eslaminejad, et al., 2006; Karamzadeh, et

al., 2012; Zomorodian, Baghaban Eslaminejad, 2012). The benefit of being able to use cells that are derived from a patient's own body is that transplantation will not elicit a host immune response. In addition, several studies suggest that MS cells induce immunomodulatory effects, which suggests that even allogeneic transplantation of these cells would not trigger the host immune response (Shi, et al., 2011).

In the past MSC transplantation has been performed for different diseased tissues (Emadedin, et al., 2012; R. Fekrazad, et al., 2015; Reza Fekrazad, et al., 2016). However, in 2007 Masaki et al. experimented with neonatal mice and compared the application of bone marrow mesenchymal stem cells (BM-MSCs) and limb bud transplantation into amputated limbs. They demonstrated that both BM-MSCs and limb bud transplantation form the segmented pattern of bone and cartilage which is crucial to regeneration (Masaki, Ide, 2007).

One issue with the stem cell approach is that stem cells lack the positional information needed for regeneration to occur. It doesn't help to just have the cells grow; they need to know where to grow. Without going into too much detail, there have been a few studies that attempted to help guide the stem cells to where they belong through introducing different factors into the mix. One such study showed they can induce the formation of multi-digit frog limbs in post-metamorphic specimens (Lin, et al., 2013). Another study attempted to replicate the in-vivo niche of a multifaceted limb through genetic modification of BM-MSCs to produce blastemal-like cells. After injecting the blastemal-like cells they noticed the presence of digit patterning and they achieved complete regeneration of an amputated digit tip (Taghiyar, et al., 2017). According to this author that cell sources with BC qualities are able to provide a the highly complex signals required for regeneration (Taghiyar, et al., 2018).

Immune-Based Approach

Immune cells such as monocytes and tissue resident macrophages seem to be an important element in the regulation of tissue repair, regeneration, and fibrosis. Post injury, these cells begin to function significantly different. They begin to produce inflammatory mediators and growth factors that enable the regeneration process (Taghiyar, et al., 2018). In 2013 a study showed the important part that macrophages play in the successful development of new limbs in amphibians (Godwin, et al., 2013).

Although we noted above that it seems the more sophisticated the immune system is the less of a regenerative ability there will be, there still seems to be a role for at least some immune cells to play. Systemic macrophage depletion has been shown to prevent limb regeneration in axolotls during the first 24 hours after amputation. A study found that the depletion of macrophages caused an increase in inflammatory factors and a decrease in anti-inflammatory cytokines. In addition, certain growth factor levels decreased significantly causing dedifferentiation markers to become dysregulated and disrupted blastema formation (Godwin, Rosenthal, 2014). Another study found that a wide arity of proinflammatory and anti-inflammatory chemokines and cytokines can be found immediately after an injury in axolotl limb tissue (Godwin, Rosenthal, 2014). In addition, similar to mammalian wounds, various leukocytes travel to the site of an injury and many of them persist throughout the beginning of blastema formation. Despite this we do know that a severe inflammatory response promotes fibrosis and therefore obstructs the successful patterning needed to regenerate a new organ (Eming, et al., 2009) so it seems a proper balance needs to be achieved.

While immune-based approaches will not be able to induce a regenerative capacity in humans they may help improve other approaches when used simultaneously. To achieve the proper balance mentioned above we need to be able to distinguish subpopulations of immune cells. However, due to the lack of reliable markers we have not been able to make good progress thus far.

Genetic-Based Approach

Although there has been a "proof-of-concept" studies that indicates there is a link between genes and cell therapy in terms of regeneration as well as tremendous progress in gene-based strategies, I have not been able to find any clinical trials that have used this approach. The general idea of this approach is to genetically modify specific cells so that the cell can then regulate cell differentiation. It could be the reason why we have not seen any clinical trial is because of the lack of safe and efficient methods of doing so. On one hand, viral vectors achieve high transfection rate, but they have significant safety concerns. On the other hand, although non-viral vectors are relatively safe, they do not achieve efficient transfection rates (Taghiyar, et al., 2018). However, as new technological innovations, specifically CRISPR/Cas9, begin to show promise they may allow for clinical trials to begin. A review of gene-based therapies noted the opportunities that CRISPR/Cas9 holds because of its widely acclaimed abilities and relative ease of use (Janssen, et al., 2016). Today the vast majority of CRISPR/Cas9's use case has been in basic research (i.e. knockout mice) but that is slowly starting to change.

Conclusion

It seems probable that the future will see regeneration of complete organs and limbs. Perhaps it will be in vitro at first but eventually in vivo as well. New breakthroughs have been able to apply many of the techniques employed by species that have a natural ability to regenerate to ourselves. Whether it is the biodome or the 3D printing or tissue engineering, it seems that whatever final solution we come up with will require us to employ multiple tactics. It also seems that different organs and limbs will require different approaches a well.

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