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Review

Complement-triggered pathways orchestrate regenerative responses throughout phylogenesis

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ABSTRACT

Adult tissue plasticity, cell reprogramming, and organ regeneration are major challenges in the field of modern regenerative medicine. Devising strategies to increase the regenerative capacity of tissues holds great promise for dealing with donor organ shortages and low transplantation outcomes and also provides essential impetus to tissue bioengineering approaches for organ repair and replacement. The inherent ability of cells to reprogram their fate by switching into an embryonic-like, pluripotent progenitor state is an evolutionary vestige that in mammals has been retained mostly in fetal tissues and persists only in a few organs of the adult body. Tissue regeneration reflects the capacity of terminally differentiated cells to re-enter the cell cycle and proliferate in response to acute injury or environmental stress signals. In lower vertebrates, this regenerative capacity extends to several organs and remarkably culminates in precise tissue patterning, through cellular transdifferentiation and complex morphogenetic processes that can faithfully reconstruct entire body parts. Many lessons have been learned from robust regeneration models in amphibians such as the newt and axolotl. However, the dynamic interactions between the regenerating tissue, the surrounding stroma, and the host immune response, as it adapts to the actively proliferating tissue, remain ill-defined. The regenerating zone, through a sequence of distinct molecular events, adopts phenotypic plasticity and undergoes rigorous tissue remodeling that, in turn, evokes a significant inflammatory response. Complement is a primordial sentinel of the innate immune response that engages in multiple inflammatory cascades as it becomes activated during tissue injury and remodeling. In this respect, complement proteins have been implicated in tissue and organ regeneration in both urodeles and mammals. Distinct complement-triggered pathways have been shown to modulate critical responses that promote tissue reprogramming, pattern formation, and regeneration across phylogenesis. This article will discuss the mechanistic insights underlying the crosstalk of complement with cytokine and growth factor signaling pathways that drive tissue regeneration and will provide a unified conceptual framework for considering complement modulation as a novel target for regenerative therapeutics.

1. Introduction – overview

1.1. Current trends and challenges in regenerative medicine

Regenerative biology defines a rapidly expanding field of research that comes to terms with the very essence of organismic development; the inborn ability of cells and tissues to reprogram their fate, switch into an embryonic-like, pluripotent state, and repopulate damaged or malfunctioning organs through lineage-specific redifferentiation [1].

Regenerative responses culminate through finely orchestrated cellular processes and fate-deciding molecular circuits that are activated in response to perturbations attempting to "dismantle" tissue homeostasis. Unraveling the overarching signals, genetic and epigenetic factors, and cellular mechanisms that are recruited by tissues in order to activate their complex regenerative programs essentially amounts to understanding the evolutionary trail of cellular pluripotency, lineage-specific commitment, and cell differentiation [2,3]. The ontogenetic pathway that a cell follows resembles to a great extent the developmental blueprint of the entire organism. In this respect, the early development of all mammals proceeds through a sequence of fate-deciding stages along an irreversible pathway of restricted plasticity and increasing specialization.

The long-prevailing dogma that cell differentiation is a unidirectional process irreversibly leading to the formation of distinct

Abbreviations: ECM, extracellular matrix; DAMPs, danger-associated molecular patterns; HSCs, hematopoietic stem cells; HSPCs, hematopoietic stem-like progenitor cells; C3aR, C3a receptor; C5aR, C5a receptor; MSCs, mesenchymal stem cells; EMT, epithelial-to-mesenchymal transition; IPE, iris pigmented epithelial; MAC, membrane attack complex; RPE, retinal pigmented epithelium; CCl_4, carbon tetrachloride; PHx, partial hepatectomy; ASP, acylation-stimulating protein.

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and rigid tissue blueprints has been drastically challenged over the years through the discovery of pluripotent adult stem cells [4]. Since the seminal observations of *John Gurdon* and his nuclear transfer experiments in *Xenopus laevis* that eloquently demonstrated that the nucleus of a terminally differentiated cell can be reprogrammed epigenetically and give rise to a fertile mature organism [5], stem cell biology has expanded in new directions, paving the way for the advent of adult cell reprogramming technologies, tissue bioengineering, and regenerative medicine [6].

Regenerative medicine applies tissue bioengineering and cell replacement technologies to address the mediocre regenerative capacity of adult tissues and counteract the shortage of donor organs and generally dismal outcomes of organ transplantation. It offers great promise for ex vivo organ development through manipulation of the adult stem cell potential to drive tissue repair and regeneration processes [6,7]. Crucial to our understanding of the molecular basis of tissue plasticity and adult organ regeneration are insights provided by regeneration models developed in various phylogenetically distant species, such as flatworms (planarians), urodele amphibians, and rodents [8]. Through persistent natural selection processes, nature has taught us that the regenerative potential of adult tissues regresses significantly as the evolutionary scale draws closer to higher vertebrates. Regeneration remains in mammals as a vestigial activity that is evident only in a few fetal tissues during embryogenesis [9].

A hallmark of tissue regeneration in lower vertebrates is the elaborate tissue reconstruction program that involves coordinated morphogenetic rearrangements, dedifferentiation of adult tissue-specific cells, and precise whole-body patterning that can tailor amputated limbs to regenerate the entire structure of a fully functional organ [10]. In sharp contrast to urodele species, the regenerative responses of mammals lack the pluripotency of tissue patterning and proceed through a rather linear pathway of tissue-compensatory hyperplasia, leading to mass restoration of damaged tissues/organs (e.g., liver regeneration) [11]. Several studies have highlighted the important contribution of stem-like progenitor cells to the tissue regenerative process [12]. It is now well appreciated that stem-like progenitor cells that reside within the damaged tissues become activated by a wide array of factors released in the microenvironment of the regenerating tissue and assume the ability to differentiate along various cell lineages [13]. In several cases, these pluripotent cells are thought to act in conjunction with other parenchymal or non-parenchymal stromal cells to coordinate the regenerative response. Exceptions to this rule apply to several regeneration models in which the role of stem cells is still debatable, such as in models of liver regeneration in which parenchymal cell division accounts for tissue restoration.

Tissue regeneration culminates in the activation of multiple growth factor-triggered pathways that drive cell cycle re-entry and proliferation of previously quiescent and terminally differentiated cells of the adult body [1]. However, as with many other biological processes, the pathway of tissue regeneration is far from being unidirectional. Regenerative responses involve the concerted action of multiple biological systems and proceed through the activation of resident cells and of stem-like progenitors that either reside locally in the tissue or become mobilized and home to the tissue after being generated in the bone marrow or other peripheral organs [14]. It is now a prevalent concept in the field that tissue regeneration can manifest itself only under the dynamic interaction of stem-like, tissue-committed, stromal and immune cell-derived factors [15]. The integrity of this diverse network of interactions is thus a prerequisite for the fine execution of a tissue regenerative program.

From a therapeutics standpoint, modern bioengineering endorses the concept of a systems-wide impact on regenerative responses and aims to optimize strategies for ex vivo tissue regeneration and whole-organ replacement [7]. Biomaterial-based scaffolds are being developed as biocompatible supports for tissue reconstruction, taking into account the various spatiotemporal constraints and factors affecting cell self-renewal and coordinated proliferation. The essential elements that have to be mounted together in an ex vivo system for organ regeneration include the reprogrammed adult stem cell pool, a source of nourishing growth factors, and a biocompatible 3D-scaffold upon which cell–cell contact and interactions will be promoted [12]. These bioengineering rules ensure that proliferating cells will develop a 3-D network resembling the actual architectural tissue pattern of the intact organ [7]. Decellularized matrices based on collagen and other extracellular matrix (ECM) constituents essentially provide the regenerating cells with all the stimulants (growth factors) and regulators that will coordinate the regenerative process [16]. However, a significant limitation in further developing ex vivo systems for tissue engineering lies in the absence of a fully functional immune system that will monitor the growing tissue, as well as a lack of immune effector cells that normally infiltrate the regenerating tissue to support the cell–cell interactions that drive tissue repair and regeneration [15]. Recent studies have given new momentum to the field by highlighting the essential role of immunomodulators, such as inflammatory cytokines and innate immune pathways (i.e., complement) in the early stages of regeneration [11,17]. Accumulating evidence suggests that there is a dynamic interplay between the immune response and various tissue repair and regeneration programs. However, the fine interactions that twine together the inflammatory and regenerative cascades are yet to be fully elucidated.

1.2. Tissue regeneration, immunity, and inflammation: tales of mutual attraction?

The remarkable ability of invertebrates such as flatworms and lower vertebrates to regenerate entire body parts has been tightly linked to the presence of an immature and permissive immune system that lacks basic aspects of acquired immunity and thereby allows the promiscuous growth of regenerating tissues in the absence of tissue immunosurveillance, lymphocyte activation, and histocompatibility constraints [8,18]. In these organisms, the lack of a fully developed acquired immune response is counterbalanced by the presence of a versatile and multifaceted innate immune system that exhibits broad-range immune recognition properties [19]. Indeed, the gradual decline of regenerative potential along the evolutionary ladder leading to mammals and the modest or absent regenerative capacity of adult tissues in humans underscore *a relationship of reciprocity between the state of immune competence and an organism's regenerative potential* [20]. Several studies have highlighted a mutual interdependence of the immune system and regenerative processes, indicating that immunity may act as a double-edged sword in modulating the outcome of regenerative responses [15]. Moreover, the influence of inflammation on the regenerative program of various species often appears to be context-driven [15].

In this respect, studies in *Xenopus* employing limb amputation models have suggested that the local inflammatory response elicited upon formation of a post-amputation wound exerts an inhibitory effect on the regenerative capacity of the remaining tissue [20]. Through the developmental transition of young larvae to adult organisms and in later stages of *Xenopus* maturation and metamorphosis, the regenerative potential of developing tissues regresses significantly following the gradual maturation of the immune system [21].

On the other hand, recent evidence from lens regeneration studies in salamanders (newts) argues for a favorable role of inflammation and immunity in the regulation of regenerative responses. Induction of a local inflammatory response in the

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