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Regenerative Medicine Theme Issue

GUEST EDITORIAL

Expanding Horizons of Cellular Plasticity in Regenerative Medicine

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Historical Perspective

Ancient alchemical obsession with the elixir of life preceded historical reports supporting regeneration in some animals and certain organs, as was immortalized in the classical Greek mythology of Prometheus and the regeneration of his liver. Validity to this mythology was provided by the French scientist René-Antoine Ferchault de Réaumur in 1712, who reported the occurrence of regeneration in crayfish.[1] In 1766, Peter Simon Pallas reported this phenomenon in flatworms of the genus *Planaria*, the experimental analysis of which was published later based on the work of John Graham Dalyell in 1814 and J.R. Johnson in 1822 (reviewed by Brøndsted[2]). Additional work by Abraham Trembley and Lazzaro Spallanzani extended the idea to include a wide range of phyla in the animal kingdom, including hydra, earthworms, snails, aquatic salamanders, tadpoles and frogs (reviewed by Dinsmore[3]). Our current aspiration for regenerative medicine therefore rests on the foundations laid by studies on all of the above mentioned organisms as well as on insects and zebrafish.[3]

The inspiration for mammalian regeneration is further refined by the proceedings of developmental biology (Figure 1).[1,2,4–10] During development, the inherent physiological plasticity of stem cells and primary progenitor cells prompts the onset of differentiation in response to the appropriate stimuli, resulting in the generation of cell types that are mature and specialized and functionally integrate into organs and tissues. The fetus is widely recognized for its perfect execution of tissue regeneration that is otherwise absent in adults.[11] Do drivers of the fetal repair process exist in the adult tissue either in part or in its entirety? And if the critical elements are present, how are they silenced? Or is it true that the entire fetal regenerative apparatus is obliterated leaving the adult tissue permanently deprived? In this issue of *The American Journal of Pathology*, we present the Regenerative Medicine Theme Issue, which explores our understanding of these processes as well as current advances in experimental models. The Review articles in this collection discuss macrophage plasticity and polarization, dysfunction of progenitor cells under conditions of diabetes, stem cell plasticity, and the emerging importance of miRNA in tissue regeneration. These Reviews provide critical insight into these complex unfolding frontiers of regenerative medicine.

Cellular Plasticity

Emerging evidence suggests a turning back of the dial of cellular plasticity in response to injury which could include the acquisition of multipotency or a reversion to stem-like state in an effort to support tissue repair.[12] Epithelial mesenchymal transitions (EMT), under conditions of wound healing, may be considered as a classical example of cellular plasticity. This was first demonstrated by the Hungarian pathologist Ödön (Edmund) Krompercher in 1908[10] in human skin and salivary gland tumors in which basal epithelial cells in contact with hyaline were found to transition to mesenchymal cells. However, the credit for the discovery of this phenomenon was given to Greenburg and Hay[13] for studies performed in adult and embryonic anterior

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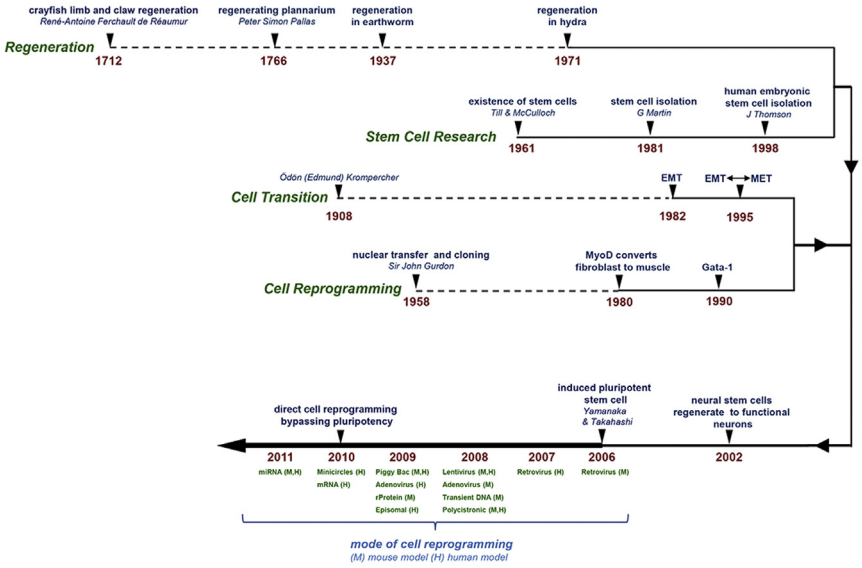

Figure 1 A schematic timeline of the history of regeneration, stem cell research, cellular transition, and cell reprogramming. Although these areas of research were initially considered to be different, they now form an integral part of regenerative medicine.[1,2,4–10]

lens tissue. Such cellular transition is commonly exhibited not only by stem cells but also by blood-borne monocyte-derived macrophages. Das et al[14] have addressed the significance of plasticity in macrophages and monocytes and their relevance to tissue regeneration and repair.

The search for transcription factors determining cell fates and reprogramming in mammals has been an ongoing quest boosted by the identification of Yamanaka factors, which were found to revert terminally differentiated cells to a pluripotent state. Furthermore, study of the hair follicle stem cell model has led to the recognition of superenhancers, dynamic support systems that serve as platforms for transcription factor binding in the process of cell plasticity regulation. Interestingly, these super-enhancers are exquisitely sensitive to fine tuning by master regulators such as SOX-9.[15] These observations lead to the following questions: if the above-said factors may revert cell phenotype, then why and how are these factors silenced in adult systems? And in adults, can these factors be unleashed in a regulated manner to achieve tissue regeneration?

Diabetic Complications and Chronic Inflammation

Diabetic complications compromise the function of progenitor cell populations. In this issue of the *AJP*, Rodrigues et al[16] address the effects of hyperglycemic memory on stem cells and provide guidance on how to use stem cell therapy under conditions of diabetes. In scenarios where one stem cell niche malfunctions, stem cells from other compartments are recruited to repair the damaged tissue. Grossly underrated compared to stem cells, the significance of macrophage plasticity in adult tissue repair is substantial. Das et al[15] critically address plasticity of monocytes and macrophages in the context of tissue repair and regeneration. Roughly 15 years ago, the pro-inflammatory M1 and pro-healing M2 phenotype of macrophages were considered to be two distinct populations of cells. Although this dichotomous paradigm explaining macrophage phenotype perpetuated for the better part of a decade, experimental observations challenging this overly simplified model continued to mount. It was soon recognized that M1 macrophages may transition to reparative M2 phenotype under supportive conditions.[17] These conditions that hold the key to the resolution of inflammation are of extraordinary interest.[18,19] Under pathological conditions such as diabetes, incompetence of the stem cell apparatus is further complicated by an arrest of M1 → M2 polarization resulting in accumulation of macrophages stalled in M1 and presenting a state of chronic inflammation.[20] Advancing M1 to M2 under conditions of diabetes represents a productive approach to break the deadlock of chronic inflammation and to resume the healing process.

Macrophage Fate at the Site of Tissue Repair

Current understanding of macrophage transdifferentiation is mostly supported by observations on cellular transition with cells co-expressing macrophage and endothelial markers. Although in some cases evidence from lineage tracing studies are present, the mechanistic underpinnings defining macrophage plasticity remain obscure. Examples of such plasticity include transdifferentiation of macrophages to endothelial progenitor cells to support tissue vascularization.[21] Transdifferentiation of monocytes and macrophages to functional endothelial cells has been demonstrated by overexpression of proteins like vascular endothelial growth factor (VEGF)[21] and pleiotrophin.[22] This *in vivo* reprogramming of cellular identity using direct transdifferentiation strategies has been also demonstrated in the mouse brain,