The Aging Kidney Phenotype and Systemically Derived Stem Cells

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The desire to extend lifespan and health has occupied the scientific and lay communities during most of recorded history. This quest includes the search for some magical elixir: Ponce de Leon vainly sought the legendary Fountain of Youth in Florida, and charlatans continue to sell potions that promise longevity. Another tack in legends, novels, and history is the belief that youth could be maintained by taking a young partner, in hopes that living tissues or cells could transfer youth. The downside of this was the fear that having an aged partner could drain youth. These two approaches to aging perseverate in modern biology.

Fortunately scientists have taken up this challenge using modern ideas and methods. The source of humoral factors or cells that might be involved in either the repair of renal injury or the normal replacement of parenchymal cells is now a topic of considerable research and debate. In part, the debates may result from the fact that the models chosen to examine the questions have been quite diverse, namely organ development, responses to acute injury, or those related to the more orderly process of cell turnover as a part of normal postnatal aging. Because each of these processes may excite unique and time-dependent responses, it is important to focus experiments and their interpretation quite clearly.

Humoral factors affect tissue repair in both aging and acute kidney injury. A series of parabiotic experiments involving aged and young mice provided evidence that some humoral factors were passed between the young and old mouse that restored skeletal muscle satellite cells, a skeletal muscle progenitor cell, and some of the phenotypic changes of aging in the aged mouse toward normal values. Although the humoral substances could have been derived from the young donor and passed to the aging recipient, it remains possible that the young partner was also able to handle some toxic metabolite that accumulates in aging. Candidates for such substances include advanced glycation end products, because they accumulate in aging and result in phenotypic changes resulting from depletion of cellular antioxidant mechanisms.

The concept that soluble factors are important in tissue regeneration is also extended by the observation that diffusible factors derived from macrophages in ischemia-perfusion injury foster regeneration of tubular cells. Thus, phenotypic changes in parenchymal cells with aging could be influenced by changes in distant organs or in the behavior of migrating cells.

The source of cells that might be involved in either normal turnover of kidney parenchymal cells or their response to injury has been recently reviewed. The experiments from the laboratory of Fogo and colleagues in this issue of JASN extend previous studies showing both that the aging phenotype to young mice could be transferred by bone marrow transplantation (BMT) and that at least some of the glomerular changes in aging could be reduced. The current study addresses this problem by using male donors and examining recipient kidneys for the Y chromosome. Although some previous studies did not include lineage tracing, mesangial cells isolated from the glomeruli of young recipients of marrow transplants from old mice had a similar phenotype to mesangial cells isolated from aging mice. More convincing evidence of the transfer of a specific sclerosis-prone phenotype and genotype was provided in earlier studies from the same laboratory, in which the glomerular phenotype depended on the genotype delivered with transplanted bone marrow and the number of cells with that phenotype that repopulated the glomeruli. These studies were extended to another form of glomerulosclerosis, diabetic nephropathy, in which the sclerotic lesion, but not the hyperglycemia, was transferred to the recipient by BMT. Because mesangial cells isolated from the recipients expressed both an altered phenotype and genotype and glycemia remained normal, this report additionally suggested that not all organs were repopulated by BMT. In summary, repopulation of the glomeruli and transfer of a disease phenotype by BMT have been shown in two different models of glomerulosclerosis, in normal aging, and in a model of IgA nephropathy.

The current study uses 129SvJ mice and examines a number of phenotypic changes that had not been previously studied,
including Klotho, markers of senescence, and markers of epithelial-mesenchymal transition. Although caution should be used in comparing aging changes across mouse strains, as well as generalizing findings in animal models to humans, these elegant studies confirm and extend previous studies. They also suggest that a more detailed study of bone marrow cells might prove to be an area of future investigation for the understanding and management of both normal aging and the causes of renal disease in the offspring of mothers with conditions that predispose them to conditions such as obesity, hypertension, or diabetes.22

The origin of regenerating cells in the kidney tubules after injury could also be from stem cells thought to be localized to the papilla23,24 or from proliferation of local cells.3 Injured cells were shown to proliferate and take on properties not ordinarily associated with mature cells, such as phagocytosis.3,25 Whether phagocytosis of antigen-antibody complexes was induced in mesangial cells was examined in Chediak-Higashi mice, using BMT. This study found that the complexes were principally taken up by cells containing giant lysosomes,26 suggesting that macrophages derived from the Chediak-Higashi bone marrow donor were the principal phagocytic cells in the mesangial region.

The further question is whether the findings of the current study can be applied to the aging kidney in humans. Namely, is the nephrology field ready to address kidney aging experimentally or clinically using bone marrow transplantation? A note of caution is that the data from the current study17 and from the others cited above suggest that normal aging is associated with phenotypic changes in bone marrow cells, and this could also apply to stem cells isolated from other adult tissues. Apart from this issue, one cannot utilize stem cells without selection for the targeted organ without the risk of tumor development. The fact that preselection of mouse embryonic cells expressing renal tubular markers resulted in localization of precursors into multiple tubular segments after intrarenal injection, without tumor formation, suggests that this approach might be feasible in the future.27

Even if the utilization of kidney-specific stem cells were to be realized, which cell(s) would one choose to replace or repair? Because it appears that stem cells (of progenitors) home to specific niches and most tissue segments have unique niches, selecting the appropriate cell(s) to deliver to the affected individual could prove to be a challenge. At the very least, considerable research in this area would be necessary before embarking on such a project.

Finally, the whole question about the nature, causes, and the significance of kidney aging is the subject of current debate.28–31 This complicates the issue of who, if anyone, should be considered for stem cell therapy. Although the costs might be initially high, the fact that generic renal tubular cells selected for specific segments of the kidney might be available in the future from one of the several companies that furnish stem cells suggests that this could possibly be an approach for the future.

In summary, the current study is timely, extends and validates previous work in the area, and suggests that there is both a need and an opportunity for developing new areas of investigation on the topic of the source of regenerating cells in the injured kidney and in chronic disease processes such as diabetes and aging.

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DISCLOSURES

None.

REFERENCES

Fishing for New Glomerular Disease-Related Genes

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Identification of new disease-related genes contributing to various forms of glomerular pathobiology is a critical step leading to the development of novel treatments and therapies for kidney-related disorders. Significant progress toward this end has been realized by contributions from the Matrix Biology group at the Karolinska Institutet, led by Karl Tryggvason. Several years ago, gene-profiling methods were used to identify genes that show significantly elevated levels of expression in the renal corpuscle. A series of ensuing publications validated these findings with in vitro and in vivo methods, combined with extensive data-mining efforts to describe highly expressed transcripts and protein-protein interactions occurring in the glomerulus. The end result was the creation of GlomBase and GlomNet.1–3 GlomBase identified over 300 novel transcripts having elevated glomerular expression but with ill-defined function. The need for an efficient, reliable, and relevant method to evaluate these candidate genes in determining their potential for interrogating glomerular disease is crucial. One such relevant animal model that has already proven invaluable in providing data for functional studies in a number of organ systems is the zebrafish (Danio rerio).4,5

A systematic investigation into the role these genes may play in glomerular development and disease is currently underway. A recent article originating from the Tryggvason group identified the epithelial polarity gene, crumbs (crb2b), as having a critical role in maintaining the integrity of the podocyte slit diaphragm.6 This article highlighted the usefulness of the zebrafish in obtaining functional data when interrogating a specific gene. In the current issue of JASN, Nishibori et al. report on another one of the more than 300 genes originally identified by this group.7

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