

brane and/or transition fiber regulation might be detrimental for ciliogenesis and correct positioning, resulting in the observed phenotype of the double mutants. Many key questions remain unanswered. Even though MKS1 and MKS3 physically interact, it is unclear how they act to regulate ciliogenesis, cilia length control, or cilia number. In mammals, MKS3 function regulates the number of cilia on the apical membrane in kidney tissues *in vivo* and *in vitro*, and loss of MKS3 results in an increased number of cilia. The authors of this study do not comment on cilia numbers, which may reflect a difference between a mammalian and nematode role of MKS3. Along this line, MKS3 might play additional roles in mammals *versus* nematodes, on the basis of its differential localization. Elucidating the function of MKS3 will also require investigating its potential genetic interaction with other ciliopathy genes, which would give important insights into the understanding of the pathogenesis of the cystic phenotype.

Several reports recently provided data indicating that phenotypic severity among MKS and NPHP is a consequence of mutational load, meaning that MKS and NPHP lie within a phenotypic continuum rather than represent multiple distinct clinical entities and that the sum of mutations in ciliary genes define the severity of the phenotype. Further studies of MKS3 in conjunction with other ciliary proteins are now required to unravel how different mutational loads can lead to the clinical variability observed in patients with MKS as well as other ciliopathies and identify further, second-site modifiers.

This study by Williams *et al.*<sup>12</sup> offers a deeper understanding of the importance of mutational load on the presentation and severity of ciliopathies and expands the understanding of the synergistic interactions between ciliopathy genes. Further analysis will hopefully allow targeted therapies to alleviate the morbidity and mortality associated with these devastating diseases.

## DISCLOSURES

None.

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See related article, "Normal Ciliogenesis Requires Synergy between the Cystic Kidney Disease Genes MKS-3 and NPHP-4," on pages 782–793.

## From Proteus to Prometheus: Learning from Fish to Modulate Regeneration

Paola Romagnani

Excellence Centre for Research, Transfer and High Education for the Development of *De Novo* Therapies, University of Florence, Florence, Italy

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Abraham Trembley discovered hydras swimming in a stream near The Hague in 1740. By dissecting and watching them regenerate

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**Correspondence:** Dr. Paola Romagnani, Department of Clinical Pathophysiology, Nephrology Section, University of Florence, Viale Pieraccini 6, 50139, Firenze, Italy. Phone: ++39554271356; Fax: ++39554271357; E-mail: p.romagnani@dfc.unifi.it

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under the microscope, he described one of the most remarkable phenomena in biology.<sup>1–4</sup> Regeneration is a trait seen in most major branches of the animal kingdom, including urodeles and fish, although many higher species, such as humans, have only limited capacity. Some suggest the ability to regenerate tissue fully attenuates during evolution, when advanced complexity, requiring the management of vast numbers of cell lineages, integratively forms and maintains a stable body plan.<sup>1–4</sup> In the kidney, for example, the emergence of numerous populations of specialized renal epithelial cells along a segmented nephron likely represents this advanced complexity.<sup>5</sup>

The loss of full regenerative capacity is evidently the price we pay for achieving a functional complexity typical of higher vertebrates. Some of this regenerative competency, however, is preserved in specific lineages of cells that can be recalled to maintain tissue integrity.<sup>6–9</sup> Cells deputed to regeneration are indeed observed in all mature organs and are named stem cells because of the variety of cells that can stem from their lineage. Stem cells of all multicellular organisms share two universal properties: They self-renew and generate the progeny of differentiated cells.<sup>1–4</sup> Accordingly, comparative genomics unravels the molecular and functional similarities of stem cell biology not only within the animal kingdom but also across kingdoms.<sup>1–4</sup> Although the blueprint is far from complete, it is obvious that stem cell systems at the base of metazoan evolution are important in identifying basic mechanisms of stem cell biology in mammals and, more important, in humans.

In this issue of *JASN*, de Groh *et al.*<sup>10</sup> advance on lessons from zebrafish to learn how to modulate the regenerative potential of kidney tissue. The authors designed a library of small molecules and screened them for effects on renal regenerative capacity.<sup>10</sup> The zebrafish is an ideal genetic and developmental model for dissecting the molecular mechanisms of renal progenitor cell function because of the anatomic simplicity of its nephrons compared to the multitudes of nephrons in a mammalian kidney.<sup>11</sup> From a functional standpoint, these fish nephrons consist of a blood-filtering renal corpuscle, proximal and distal tubular regions, and the pronephric duct.<sup>11</sup> During zebrafish development, bilateral strips of intermediate mesoderm lying on either side of the trunk undergo a mesenchymal-to-epithelial transition to form the pair of pronephric nephrons. The anteriormost renal progenitors differentiate into podocytes, which migrate medially and fuse at the midline to form a single renal corpuscle. The nephrons also fuse posteriorly at the cloaca to form a shared exitway. In the study by de Groh *et al.*, treating zebrafish embryos with a novel chemical compound, 4-(phenylthio)butanoic acid, induced proliferation of renal progenitor cells, an effect related to its ability to act as a histone deacetylase (HDAC) inhibitor.<sup>10</sup>

In eukaryotic cells, DNA is wrapped around core histones to form nucleosomes that fold into higher order chromatin. Modification of histone N-terminal tails through acetylation or deacetylation alters the interaction between histones and DNA. HDAC inhibitors regulate the transcription of cell type-specific genes by modulating this accessibility to chromatin<sup>12</sup> as well as the

extensive self-renewal of mouse and human embryonic stem cells.<sup>13</sup> Previous studies also described a role for HDAC inhibitors in the maintenance of balance between self-renewal and differentiation in other adult stem cell systems.<sup>12</sup> Given their effects on stem or progenitor systems, HDAC inhibitors are possible pharmacologic modulators of regeneration.<sup>12,13</sup>

The study of de Groh *et al.*<sup>10</sup> suggests these considerations might also extend to the kidney. The recent description of renal stem cells in adult human kidney<sup>3,6–9,14</sup> and their strict phenotypic and functional similarity with embryonic renal stem or progenitor cells further support this possibility.<sup>3</sup> Interestingly, very recent studies also reported that treatment with HDAC inhibitors reduces epithelial-to-mesenchymal transition<sup>15</sup> and fibrosis in obstructive nephropathy,<sup>16</sup> regulates bone morphogenic protein 7 in the regenerative response to ischemia,<sup>17</sup> and prevents the progression of accelerated nephrotoxic serum nephritis toward glomerulosclerosis.<sup>18</sup>

The central role of stem or progenitor cells in maintaining the integrity and functionality of organ tissues also suggests their manipulation might engender adverse effects.<sup>12</sup> Indeed, zebrafish larvae treated with HDAC inhibitors develop edema,<sup>10</sup> which suggests that deregulated expansion of renal progenitor cells can disrupt organ regeneration or function. These expanded progenitor populations, in fact, fail to migrate medially and fuse at the midline to form a glomerulus, an effect that seems related to the lack of terminal differentiation toward the podocyte phenotype.<sup>10</sup>

Taken together, these results advance a novel concept—that manipulating kidney regeneration is possible—but may also be harmful without deeper knowledge of the diverse properties of renal progenitor cells unleashed. Thus, understanding the mechanisms and devising improved approaches to control cell fate and function *in vitro* and *in vivo* are crucial for translating stem cells and their modulators into the clinic.

Chemical compounds that modulate site-specific targets that control signaling pathways or epigenetic events<sup>19</sup> may represent useful tools for manipulating cell fate and offer some advantage over genetic manipulation. For example, in contrast to genetic manipulation, the effects of chemical compounds are typically fast and reversible, providing more precise temporal and context-dependent regulation of protein function.<sup>12,20</sup> These effects can also be finely tuned by varying the concentration or combination of drugs of interest. In addition, the wide structural and functional diversity endowed by synthetic chemistry potentially will let us target specific molecular interactions or cellular functions more precisely.<sup>12,20</sup>

Stem cells offer significant promise for developing treatments for many human diseases or injuries. The challenge faced currently by regeneration science is to identify ways to instruct stem cells and their progeny to undergo proper development, including migration to the site of damage, differentiation into specific cell types, establishing correct anatomic connections and physiologic functions, and surviving long term. Now, the challenge has also started for the kidney: It is time for regenerative nephrology.

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## DISCLOSURES

None.

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See related article, “Inhibition of Histone Deacetylase Expands the Renal Progenitor Cell Population,” on pages 794–802.

## Variations in Mortality among Hospitalizations for Acute Kidney Injury

William M. McClellan

Departments of Medicine and Epidemiology, Emory University, Atlanta, Georgia

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Health insurance, setting of care, geography, and primary disease all affect mortality among various populations in the United States.<sup>1,2</sup> If medical care for these different populations were truly comparable, then we might expect similar mortality outcomes and attribute differences to random variation. Unfortunately, population-to-population variations in mortality are frequently observed and persist even after controlling for individual patient characteristics. This suggests potentially remediable differences in the content, organization, and delivery of health care may be important in shaping true variation.<sup>3–6</sup> Such modifiable differences in health care–related mortality, if they exist, warrant special attention as clinical and public health problems.

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**Correspondence:** Dr. William M. McClellan, Departments of Medicine and Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA 30220. Phone: 404-727-6976; Fax: 404-727-8737; E-mail: [wmcclel@sph.emory.edu](mailto:wmcclel@sph.emory.edu)

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