Reprogramming Somatic Cells to a Kidney Fate

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Summary: Recent years have challenged the view that adult somatic cells reach a state of terminal differentiation. Although the ultimate example of this, somatic cell nuclear transfer, has not proven feasible in human beings, dedifferentiation of mature cell types to a more primitive state, direct reprogramming from one mature state to another, and the reprogramming of any adult cell type to a pluripotent state via enforced expression of key transcription factors now all have been shown. The implications of these findings for kidney disease include the re-creation of key renal cell types from more readily available and expandable somatic cell sources. The feasibility of such an approach recently was shown with the dedifferentiation of proximal tubule cells to nephrogenic mesenchyme. In this review, we examine the technical and clinical challenges that remain to such an approach and how new reprogramming approaches also may be useful for kidney disease.
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To reprogram, as the word suggests, is to re-impose a different state; to program again or differently. In the context of cell biology, this term is used to refer to the reconfiguration of the epigenetics of a cell.[1] It is this epigenetic program that dictates the genes being expressed in any given cell state and hence the phenotype of the cell. During the process of differentiating into a specialized adult cell type, such as the hepatocyte of the liver or the proximal tubular cell of the kidney, a series of epigenetic marks are put in place to specify which pathways are active and which are silenced. Although differentiation of a cell was long assumed to be a permanent process, the capacity for cells to be reprogrammed, and hence for epigenetic marks to be added or removed, is now accepted. In the case of imprinted genes, for example, the allele of a given gene inherited from the father may be silenced whereas the allele inherited from the mother remains active. This has long been appreciated, as has the need for this imprinting to be reprogrammed in the gametes.[1] Indeed, the ultimate reprogramming event was shown by John Gurdon[2] in 1962 when he showed that the egg plasm of an enucleated frog egg was sufficient to reprogram adult epithelial cell nuclei back to the starting state of the original egg nucleus; a process called *nuclear reprogramming*. The application of this finding as a somatic cell nuclear transfer (SCNT) led to the birth of Dolly the sheep, the first cloned mammal, in 1996.[3] However, successful SCNT has proven challengitng in many species including human beings, and, in many countries, SCNT for reproductive purposes remains illegal in human beings.

Although the concept of reprogramming has been with biology for some time, the plasticity of the adult somatic cell state generally was regarded as low to nonexistent. However, studies dating back almost 20 years began to show that one adult cell type could be convinced to change fate (reprogrammed) via the overexpression of specific transcription factors. Hence, a pre–B cell could become a macrophage[4,5] or a fibroblast could become a myoblast.[6] This type of transdifferentiation (one mature state to another) or dedifferentiation (one mature cell type to a more primitive state in the same lineage) implied that the epigenetic landscape could be modified or at least overruled. More recent studies have applied a similar approach of identifying key transcription factors critical to specific cell lineages to turn one cell type into another. We refer to this as *direct reprogramming*. It was the extension of this approach of overexpressing key transcription factors that was proven to be a major breakthrough. In 2006 in mice,[7] and then in 2007 in human beings,[8] it was shown that the enforced expression of 4 key transcription factors, *Oct4*, *Sox2*, *Klf4*, and *c-Myc*, were sufficient to reprogram an adult fibroblast back to a pluripotent state; a state equivalent not to a fertilized egg but to that of the inner cell mass of an embryo. This process, termed *induced*

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pluripotency (cells generated this way are referred to as *induced pluripotent stem cells* [iPSC]), now has been validated using a wide array of starting cell types and a panoply of different technologies for inducing gene expression.[9] Most importantly, it appears that the mechanism involves an undressing of the chromatin state that, although not exactly representing a step back through all prior decisions made during the lifetime of that cell, renders the cell malleable during reprogramming to differentiation in another direction.[10,11] This final approach, referred to as *partial reprogramming*, opens up the prospect of being able to turn any cell type into any other cell type.[12–15]

Although still in its infancy, reprogramming technology is becoming increasingly established. With reprogramming comes the possibility of generating any desired cell type either for drug screening, disease modeling, or for the repair or regeneration of organs in a diseased state. Indeed, the latter possibility may deliver alternate regenerative therapies to combat a range of diseases with multifactorial etiologies. Chronic kidney disease (CKD) is one such complex disease that would benefit greatly from a regenerative therapeutic approach. The incidence of CKD in society is increasing rapidly, as is the burden of this disease on our health care system.[16] At present, treatment options for CKD are limited to dialysis and/or transplantation, but the increasing financial strain of providing these treatments and the steady decrease of suitable donor organs highlights the desperate need for novel therapeutics. In this review, we provide an overview of the field of cellular reprogramming, describe the progress to date as this technology applies to the kidney, and discuss the challenges ahead for the application of such approaches to clinical nephrology.

NUCLEAR TRANSPLANTATION: EVIDENCE FOR THE CAPACITY TO REPROGRAM A CELL

As noted previously, the first evidence for the reprogramming of an adult somatic cell came from transplantation of fully differentiated cell nuclei into enucleated fertilized frog eggs.[2,17] The transferred nuclei came from differentiated frog intestinal epithelial cells and were capable of producing fully functional tadpoles upon transplantation into an enucleated egg.[2] This discovery led to the conclusion that mature cell nuclei were able to return to a nonlineage committed (pluripotent) state when gene activity was changed by nuclear transfer. From this observation came the technology of SCNT in organisms other than amphibians. Dolly the sheep was generated by transplanting a single mammary gland cell nucleus from an adult sheep into an enucleated egg from another sheep,[3] establishing the transferability of this form of reprogramming in mammalian cells. Although the mechanism underlying nuclear reprogramming is still not fully understood, key observations provide clues. First, the success rate of nuclear reprogramming decreases when a donor cell is derived from older adult.[2] Second, global chromatin decondensation leads to an increase in the volume of the transferred nucleus caused by the egg protein, nucleoplasmin.[18] In addition, the linker histone H1 of the transferred somatic nucleus is replaced by that of the recipient oocyte to open the chromatin.[19] Third, histone deacetylation inhibitors, such as valproic acid (VPA) and trichostatin A, improve the success rate of SCNT in the case of mouse oocytes,[20,21] suggesting a requirement for histone modification. Fourth, during nuclear reprogramming, a global reversal of DNA methylation is induced to reactivate silenced genes such as *Oct4* and *Nanog*.[22] Taken together, these observations suggest that egg proteins are responsible for the chromatin remodeling of the transferred somatic nucleus, resulting in histone modification followed by DNA demethylation, and resulting in the erasure of somatic epigenetic memory. Although application within livestock breeding for the cloning of desired traits is attractive, SCNT (even if restricted to the generation of early embryos for the harvesting of pluripotent cells) has not been applied to human regenerative medicine. Aside from barriers including ethical concerns and legal restrictions on reproductive cloning in human beings, the technology has not proven successful in a human setting. Where possible, the generation of desired cell types using SCNT would require a source of oocytes and the generation and subsequent destruction of an early embryo, an undesirable approach given our current understanding of alternatives. Despite this, what has been learned from SCNT has led the way to other approaches for cell reprogramming.

EVIDENCE FOR TRANSCRIPTION FACTOR–BASED DIRECT REPROGRAMMING

The first evidence of reprogramming using transcription factors was reported in 1987.[6] They identified 92 complementary DNAs specifically expressed in myoblast using complementary DNA subtraction between the C3H10T1/2 mouse embryonic fibroblast cell line and 5-azacytidine treated (aza)-myoblast lines cloned from C3H10T1/2. The overexpression of one of these genes, the transcription factor *MyoD*, converted C3H10T1/2 to myogenic colonies. Although other fibroblast and adipoblast cell lines similarly were converted to myoblasts in response to *MyoD*, they could not conclude that this transcription factor was a master myogenic gene because some cell types, including the monkey kidney cell line, CVl, did not undergo myogenic

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