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Editorial

Renal endogenous stem cells: a new source for regenerative medicine in preterms?

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From the womb to the adult
Guest Editors: Vassilios Fanos (Cagliari, Italy), Michele Mussap (Genoa, Italy), Antonio Del Vecchio (Bari, Italy), Bo Sun (Shanghai, China), Dorret I. Boomsma (Amsterdam, the Netherlands), Gavino Faa (Cagliari, Italy), Antonio Giordano (Philadelphia, USA)

The purpose of playing…
Is to hold the mirror up to nature
William Shakespeare, *Hamlet*, *III. II.*

Keywords

Kidney, stem cells, regenerative medicine, prevention, therapy.

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The creation of new medical approaches based on stem cells to treat chronic kidney disease (CKD) and in particular end stage renal disease (ESRD) has become imperative in recent years, due to the significant burdens of patients affected by renal failure and to the limitations of dialysis and kidney transplantation to solve the problem [1]. The initial prospective of utilizing stem cells for regenerating the affected kidney has been at the basis of excitement and hope for all patients affected by ESRD [2]. Unfortunately, too many challenges have halted the possibility to make such regenerative approach a reality, and the vast majority of patients with CKD and renal insufficiency experience a reduced quality of life associated with high mortality [3]. The problem appears particularly severe when ESDR develops in childhood. Children submitted to kidney transplantation have a 95% of survival rate at 5 years, but only 66% of them survive at 20 years after renal transplant [4]. As a result, patients transplanted in childhood will need repeated renal transplants during their life.

But, why regenerative medicine failed to become the definitive therapy for ESRD? And which is the explanation of the inability of the traditional regenerative medicine to give a new chance to the multitude of patients affected by CKD? Our opinion is that renal regenerative medicine might experience a major renaissance in the next years, developing new methodologies stemmed from the previous attempts. Here, we present some major points to be addressed, in order to open a debate on the potential offered by the different regenerative methodologies.

1. *The "exogenous" approach.* Several potential therapeutic methods based on the use of stem cells have been reported in recent years, all aimed at regenerating the renal parenchyma in diseased kidneys [5]. In the majority of regenerative methodologies, exogenous stem cells have been utilized. The direct application of exogenous embryonic CD24+ stem cells has been proved to induce their engraftment into damaged tubules in an experimental mouse model of kidney disease [6]. In that study, the activation of the Wnt/beta-catenin signaling pathway was found to be required for driving the new nephrogenesis [7]. Mesenchymal stem cells have been used, with the aim to treat chronic renal failure [8]. A promising therapeutic approach for patients with ESRD has been identified in *de novo* kidney regeneration utilizing exogenous stem cells [9].
2. *The "endogenous" approach.* The activation and mobilization of endogenous stem cells represents the last and, in our opinion, more promising technique in renal regenerative medicine. Emerging evidences are surfacing in the recent years introducing a new concept in nephrology: the human kidney possesses innate regenerative abilities, even in adulthood [10]. Studies in animal models have shown the existence of tubular repopulation following renal damage caused by gentamicin [11], suggesting the persistence of multipotent stem/progenitors in the adult kidney. These data have been confirmed in recent years, by the isolation of renal progenitors in the adult human kidney [12, 13].
3. *The "therapeutic" approach.* The vast majority of regenerative methods proposed in the literature has been developed for and applied to adult subjects with severely damaged kidneys. Problems related to the integration between the newly-formed nephrons and a totally disrupted renal architecture may be at the basis of the inability of the traditional renal regenerative medicine to completely regenerate the damaged kidney. This suggests that a new approach is mandatory.
4. *The "prevention" approach.* A new emerging hypothesis surfaces in the literature in recent years: the "physiological" renal regenerative medicine [14]. This new approach is based on the following data: a) premature and low birth weight infants have a low nephron burden at birth that will render them susceptible to develop renal disease later in life [15, 16]; b) the kidney of premature infants is characterized by a huge number of active stem cells, that are silenced few weeks after birth [17]; c) on these so numerous and active renal stem cells, we might act soon after birth, with a regenerative approach [18] forcing them to continue nephrogenesis till to the 36th post-conception week [19-21]. This regenerative intervention might transform individuals susceptible to develop renal disease later in life into resistant individuals.

Coming back to the sentence of William Shakespeare, we think that it is time for nephrologists and perinatologists to hold the mirror up to endogenous renal stem cells, that are present in high quantity in preterms and in discrete quantities in the adults. A preventive approach in the perinatal period might decrease the number of patients affected by ESRD, encouraging the

attempts aimed to induce regeneration in adult patients with CKD. Together with traditional studies [22, 23], studies focused on the accurate analysis of the complex processes regulating nephrogenesis in the fetal life inside the renal stem cell niches (as the study from Gerosa et al. in this issue of the *Journal of Pediatric and Neonatal Individualized Medicine* [17]) may play an important role in this challenge toward a fantastic goal of the scientific community: to halt the spread of renal failure around the world.

Declaration of interest

The Authors declare that there is no conflict of interest.

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