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Review

Renal stem cells and their implications for kidney cancer

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ABSTRACT

The renal cell carcinomas (RCC) denote a diverse set of neoplasias with unique genetic and histological features. The RCCs emanate from the renal tubule, a highly heterogeneous epithelial structure, and depending on which cell is malignified the resulting cancer displays unique characteristics. Notwithstanding this, the cells of origin for the RCC forms are far from established, and only inferred by the accumulated weight of marker similarities, not always providing an unequivocal picture. The tubular epithelium is normally mitotically quiescent, but demonstrates a considerable regenerative capacity upon renal injury. Recently the hypothesis that regeneration is driven by adult stem cells has been added experimental support, providing further complexity to the issue of renal carcinogenesis. Whether these cells are linked to RCC is an open question. In the present review we therefore present the prevailing theories regarding kidney regeneration, since a better understanding of this process might be of relevance when considering the different malignancies that arise from kidney epithelium. Our own results show that papillary renal cell carcinoma displays considerable similarities to proximal tubular progenitor cells and we suggest that this tumor form may develop in a multi-step fashion via benign renal adenomas. The putative connection between renal stem cells and carcinomas is, however, not clarified, since the current understanding of the renal stem cell system is not complete. It is clear that the efforts to isolate and characterize renal progenitor/stem cells suffer from numerous technical limitations and that it remains likely that the kidney harbors different stem cell pools with a restricted differentiation potential.

1. Adult stem cells

Stem cells are undifferentiated cells characterized by their dual ability to self-renew and differentiate into diverse and specialized cell types. This definition encompasses cells of varying lineage potential, running the gamut from totipotent embryonal stem cells capable to develop into all embryonic and extra-embryonic tissues, via the more restricted multipotent stem cells producing two or more mature cell types, to unipotent stem cells. The latter two categories are encountered in stem cell populations of adult organs. Progenitor cells are regarded as an intermediate cell type between stem cells and differentiated cells, although this category blends to a degree with the properties of unipotent stem cells. Adult somatic stem cells have been most thoroughly characterized in tissues with rapidly dividing cells, such as bone marrow, or in the epithelia of intestine and skin. In these tissues, the existence of somatic stem cells is an obvious prerequisite for the life long capacity of tissue maintenance and homeostasis. The rapid kinetics of cell turnover has allowed for a detailed definition of the stem cell compartments of these tissues, whereas in organs of lower cell turnover, such as the liver or kidney, the knowledge and characterization of stem cells develops more slowly and their role in tissue repair is less evident. The stem cells of adult tissues display a strict hierarchy with a delicate and highly niche dependent balance between self-renewal and differentiation into a relatively restricted number of cell types that comprise the respective organ. The work of Takahashi and Yamanaka has added a new dimension to the stem cell model, however, showing that the hierarchical organization of somatic differentiation is not as fixed as previously thought. In their seminal paper from 2006 they could show that introduction of four transcription factors (Oct-4, c-Myc, Sox2 and Klf4), could induce pluripotency in somatic mouse fibroblasts [1]. Facsimile experiments confirmed that also human induced pluripotent stem cells could be obtained by similar means [2–5]. The concepts established in these studies have of course extraordinary potential for clinical applications but also indicate that the demarcation lines between stem cells, differentiation and cellular specialization are not a clear-cut as previously thought. This ambiguity also has some bearing when discussing cancer stem cells, as indicated below.

Abbreviations: CSC, cancer stem cell; EMT, epithelial-to-mesenchymal transition; ARI, acute renal injury; BMSC, bone marrow derived mesenchymal stem cells; CCRCC, clear cell renal cell carcinoma; SP, side population; pRCC, papillary renal cell carcinoma; PEC, parietal epithelial cells.

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2. Tumor heterogeneity and the concept of cancer stem cells

It is an established fact that neoplastic tumors display a considerable degree of cellular heterogeneity. This is to a large extent explained by the diversity of distinct cell types present in a tumor, ranging from fibroblasts, endothelial cells and immune cells to the actual tumor cells. It has also been noticed, however, that within the tumor cells proper a considerable cellular heterogeneity exists. This heterogeneity amongst neoplastic cells in a given tumor was for a long time explained by the so-called clonal selection theory [6]. This states that tumor cells accumulate genetic changes over time, allowing mechanisms of Darwinian evolution to drive clonal expansion, and simultaneous tumor progression. According to this scenario, a solid tumor is composed of a limited number of clones. Within each clone all cells have an equal capacity for survival and expansion during for example a selection pressure imposed by the immune system or during treatment with cytostatic drugs. This view has been challenged during recent years by the so-called cancer stem cell (CSC) theory [7]. According to this theory not all tumor cells have the capacity to maintain tumor growth. Based on concepts that evolved from studies of normal stem cell biology it has been suggested that tumor heterogeneity in part is a consequence of cellular diversity within the tumor, where a small subset of cells, the so-called CSCs are believed to share functional attributes with normal stem cells, such as capacity for self-renewal and differentiation into several cell types. In cancer research this field was pioneered in studies of hematological malignancies. For example, it has been convincingly shown that isolation of $CD34^+$, $CD38^-$ cells from acute myeloid leukemia enriches immensely for cells with leukemia forming capacity [8]. The studies of hematopoietic malignancies paved the way for similar analyses in solid tumors [9–17]. The progress was somewhat hampered by lack of a distinct set of differentiation markers, allowing for the robust identification of CSC from the bulk tumor cells. Furthermore the isolation of cancer stem cells from solid tissues requires harsh experimental protocols in order to obtain a single cell suspension from solid tumors. If correct, the clinical implications of the CSC theory are immense. Firstly, it may explain why current cancer treatment protocols in so many cases fail, since it postulates that the CSC subpopulation of any given tumor may be equipped with stem cell traits allowing them to escape treatment, examples of which are; slow cell cycling, increased capacity for extrusion of toxic compound and anti apoptotic signaling circuitry. Secondly, the CSC model would also explain certain aspects of metastatic spread, as this would occur through dissemination of CSC.

It is important to note that the CSC theory is mainly based on functional traits and does not imply that CSC necessarily have to be derived from normal tissue stem cells. Even though normal stem cells are endowed with attributes that would make them particularly well equipped for cellular expansion upon transformation, this could also be achieved by reprogramming tumor cells through dedifferentiation. This could be accomplished by for example hypoxia and/or epithelial-to-mesenchymal transition (EMT) [18,19]. For example, it has been shown that induction of EMT by inhibition of E-cadherin in breast cancer cells, a marker strongly associated with the epithelial phenotype, as such not only led to induction of mesenchymal traits but also enhanced self-renewal traits [19]. These observations could also serve as a bridge between the two models of cancer evolution, clonal selection and cancer stem cells, since the EMT process could occur at various stage of malignant transformation. Even though the concept of cancer stem cells remains very much debated and most likely to a varying extent is applicable to different tumor types, a prerequisite for a deepened understanding of the possible involvement of such subpopulation needs to be based on an understanding of the tissue-specific stem cells from the tissue out of which the tumors develop. In this article we will try to summarize the current knowledge of kidney stem cells and further to discuss this in relation to kidney cancer.

3. The cellular origin of kidney regeneration

The nephrons are the functional units of the kidneys and consist of the filtering glomeruli connected to the renal tubules. The tubules house some of the most energy and oxygen demanding cells of the human body. Unlike classical epithelia such as skin and the gastrointestinal tract, the normal renal epithelium is mitotically almost entirely quiescent, with an estimated single cell division per day and nephron [20]. In the wake of acute renal injury (ARI), however, the renal tubuli demonstrate an impressive capacity for regeneration, often leading to complete restoration of the tubular epithelial integrity, provided that the tubular basal membranes are intact and supportive care is instigated. It is worth pointing out that this capacity for regeneration is not always encountered in other organs, where ischemic type of injury often results in permanent cell loss and scarification/fibrosis. Nephrogenesis is the result of the interactive growth of the ureteric bud and metanephric mesenchyme, but true development of nephrons is halted before birth at week 36 [21]. In rodents the situation is similar although residual development of nephrons continues until a few days postnatally [22]. Thus, the adult human kidney is believed to lack a true multi-potent stem cell pool. Adult renal stem cell systems are not totally unknown, however, since in fish, both of the elasmobranch class (skate, sharks and other cartilaginous fish) and teleost class (skeleton based fishes) true adult nephrogenesis is encountered [23,24]. In cartilaginous fish a true nephrogenic zone is present, with the capacity to re-create lost renal tissue not only on cellular level, but also on an architectural level [24,25]. The cells of this zone show similarity to the human embryonal metanephric counterpart, and several lines of evidence indicate that the process of adult nephrogenesis in fish is indeed related to the process of embryonal nephrogenesis seen in mammals. Although clear-cut neo-nephrogenesis does not occur in mammals, it remains to be determined to what degree these exciting findings can be integrated into our current understanding of regeneration of human kidneys.

In contrast, the basis for renal regeneration in mammals has traditionally been attributed to randomly surviving terminally differentiated tubular cells [26,27]. These cells are believed to dedifferentiate by EMT, followed by proliferation, migration and coverage of the denuded tubular basal membranes, eventually reforming a polarized epithelium [28]. The initial observations supporting this concept were morphological changes upon renal injury, during which the proliferating tubular cells flatten out and show mitotic activity [29]. More recently, marker studies have been added, where the classical EMT marker vimentin has been detected diffusely in regenerating tubuli, whereas normal renal tubuli generally is negative [30]. Tubular re-expression of renal developmental markers such as Pax2 in association with regeneration lent further support for the dedifferentiation concept [31]. The discovery of stem cells in the human brain some years ago energized the search for organ-confined adult stem cells in other organs [32]. Soon, the time-honored dogma of renal regeneration based on stochastically surviving cells was challenged by reports of proper stem cells taking part in renal regeneration. These were either assigned to extrarenal sources, such as bone marrow [29,33,34], or intrarenal sites [35]. A varied experimental armamentarium has been used to identify the putative renal stem cell pool, which to a large extent can explain the rather conflicting view at hand today, since each given experimental approach has its own limitations and most likely only allows for enrichment of stem cell attributes, at best.