This extraordinary extramedullary haematopoiesis

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In this issue of the Journal, Stroo et al. [1] published their findings on the engraftment of the intact and ischaemic kidney by haematopoietic stem cells (HSC). Specifically, these investigators demonstrated that systemically administered HSC preferentially migrate to the ischaemic kidney and that this process is SDF-1/CXCR4 independent. Indeed, ischaemia-induced retention of hypoxia-inducible factor-1 has been implicated in such a preferential migration to ischaemic areas, although induction of SDF-1 was believed to be necessary [2]. This requirement for SDF-1 chemokine is overridden in leukaemic tumour niches in the bone marrow [3], but not much is known about HSC in the ischaemic kidneys. Therefore, the study by Stroo et al. published herein raises an intriguing question: Does the kidney possess a niche for HSC, considering a niche as a specialized microenvironment supporting stem cell attachment and quiescence by sheltering them from proliferation and differentiation signals, enhancing survival, regulating division and renewal, and coordinating the population of resident stem cells to meet the actual requirements of an organ [4]?

To address this question, it would be instructive to turn our attention to the embryonic development of HSC. In frog embryos, dorsal anterior mesoderm contributes progenitor cells that differentiate into haematopoietic cells found in pronephros, mesonephros, spleen, thymus and blood [5] indicating that the dorsal aorta and vasculature surrounding pronephros represent sites of maturation of haematopoietic cells. During zebrafish development, Murayama et al. [6] showed that HSC appear first between the dorsal aorta and axial vein (the homologue of aorta–gonad–mesonephros, AGM, of amniotes), migrate to dorsal haematopoietic tissue and seed the thymus and kidney. These HSC residing in AGM express CD41 (itga2b) and cmyb [7] and migrate along pronephric tubules to initiate haematopoiesis in the developing kidney. HSC isolated from teleost body kidney or head kidney but not from the spleen (using Hoechst 33342 and rhodamine-123 staining) and transplanted to lethally irradiated companion fish demonstrated the ability to reconstitute the haematopoietic system [8]. Interestingly, in elasmobranch Leucoraja erinacea, a neonephrogenic zone containing stem cell-like mesenchymal cells has been described; these cells were responsible for development of new nephrons in skates subjected to partial nephrectomy [9]. More recent findings on the origins of HSC in the AGM may shed light on these findings. Gomez’s group [10] provided evidence that embryonic haematopoiesis, before becoming contained in the bone marrow, takes place in multiple sites, kidney included, in conjunction with vasculogenesis. Most recently, Irruella-Arispe’s group [11] using genetic tracing of mesenchymal and endothelial progenitors (both present in AGM region) revealed that endothelial progenitors are capable of multilineage haematopoietic differentiation, thus establishing endothelial origin of HSC. Importantly, AGM mesenchyme is incapable of haematopoiesis, but acquires this capacity only after differentiating towards endothelial progenitors. Hence, these studies collectively argue in favour of the kidney being able to provide the microenvironment to sustain haematopoiesis, at least during embryonic development.

Does adult kidney have a similar ability to harbour HSC? Anecdotal cases on extramedullary haematopoiesis in the kidneys have been described, each emphasizing its rarity. These include by and large cases of idiopathic myelofibrosis, but also a few cases of renal cell carcinoma or anaemia due to thalassaemia [12–16].

On the molecular level, the known determinants of stem cell niches include the VLA4/VCAM-1 (endothelial adhesion) interaction, which can be disrupted by injection of neutralizing VLA4 antibodies resulting in HSC mobilization [17,18]. Interestingly, mobilized HSC downregulate the expression of VLA-4, which is also critical for firm adhesion to niches, and may hamper their engraftment [19]. N-cadherin, mainly expressed in neuronal, endothelial, muscle cells and bone marrow stromal cells, is another potential candidate for HSC adhesion and differentiation [20]. In addition, there is a school of thought that activation of matrix metalloproteases (MMP), especially the MMP-9, accompanied by cleavage of matrix proteins and exposure of cryptic adhesion sites necessary for adhesion may be also involved in processes like mobilization and homing of HSC [21]. Finally, other potential candidate ligands for HSC engraftment are hyaluronic acid, Kit ligand, selectins, osteopontin and fibronectin [22,23].

This discourse would be futile if not for the fact that HSC may play a role in kidney regeneration. Fang et al. [24] demonstrated that endogenous HSC, but not MSC,
contributed to tubular epithelial regeneration after HgCl$_2$-induced acute tubular injury. Results of various other studies showing benefits of bone marrow cells have been comprehensively reviewed [25] although two recent studies place emphasis on kidney resident rather than bone marrow-derived cells in guiding the repair processes [26,27].

What are the homing/guidance cues appearing in ischemic damaged kidney that absent in the intact organ that make it attractive for HSC homing? This is one of a series of questions awaiting to be resolved. Is it possible that after engraftment HSC differentiate and shed their typical markers, thus hampering their identification—yet another unanswered question.

Hence, although studies by Stroo et al. presented in this issue, while rejecting SDF-1/CXCR4 as one potential candidate, do not provide affirmative clues as to the molecular determinants of HSC niche in the kidney, the subject of this investigation is impregnated with exciting opportunities and promising findings awaiting basic and clinical researchers.

Conflict of interest statement. None declared.

(See related article by I. Stroo et al. Haematopoietic stem cell migration to the ischemic damaged kidney is not altered by manipulating the SDF-1/CXCR4-axis. Nephrol Dial Transplant 2009; 24: 2082–2088.)

References


