Our kidneys constitute the major foundation of our philosophical freedom. Only because they work the way they do have it become possible for us to have bone, muscles, glands, and brains."

Homer Smith (1953)

INTRODUCTION

Tissue resident stem cells are known to play a major role in the repair and regeneration of post natal organs [Anversa et al. 2003]. Despite advances in stem cell research, no definitive clues lead to a complete understanding on the regenerative potential of resident stem cells in vital organs like kidney [Hopkins et al. 2009]. Many reports have shown the presence of putative stem cells from several post natal tissues which contribute to organ maintenance and repair. Examples include epithelial stem cells in epidermis and intestinal crypts [Slack, 2000], satellite cells in muscle [Charge and Rudniki. 2004]. It is hypothesized that the presence of stem cells within organs like kidney would be of importance in possible cure of diseases [Chabbra and Brayman. 2009]. The use of progenitor cells to restore the function of damaged organs such as the heart or the kidney is a completely new therapeutic concept. However, the mechanism of action and nature of progenitor cells is not fully understood in organ regeneration.

Repair mechanisms by stem cells could include paracrine activity of the cells, neo-vascularization, and, trans-differentiation or fusion [Gnecchi et al. 2008]. The relative importance of these various mechanisms has to be determined. In addition, other mechanisms that are yet unknown might be involved. Research on the growth, regulatory mechanism and the signals of the micro environmental niche that determine its fate is very significant to harness the potential of these unique cells, which hold great hope as a prospective regenerative therapy for degenerative diseases.

Kidney is an organ with limited turnover of cells but exhibits remarkable ability to survive injury and restore function [Bahlmann and Fliser. 2009]. The precise mechanism by which adult kidney replenishes damaged cells remains to be understood. It is still not clear whether cellular repair in adult kidney is carried out by specialized renal progenitors residing in specific niches or by self-duplication/ de-differentiation of mature cells. Previous reports suggest the role of renal resident stem cells in kidney repair and

regeneration [Reviewed by Bussolati et al. 2009] and others have suggested the contribution of circulating bone marrow stem cells in renal repair [Paulsom et al. 2001]. However, limited contribution of these cells to injured kidneys has led to questions regarding their significance in kidney repair [Duffield et al. 2005]. Kidney as a mesodermal organ has been studied extensively for the complex cellular interactions of organ development [Dressler.2008]. During organogenesis, the mammalian kidney undergoes several stages of transitions and interactions between two different primordial tissues; the epithelium and the mesenchyme. The ureteric bud epithelium and the mesenchyme thus represent the key players of kidney development [Saxen et al. 1986].

In the adult kidney, EMT facilitates tissue growth and regeneration for organ repair and homeostasis. It has been reported that in an animal model of renal injury, the epithelial cells dedifferentiate to undergo mesenchymal transition during renal repair [Ziesberg et al. 2005]. Although, several studies have established that epithelial and mesenchymal populations govern kidney development and maintenance, it is still not clear which of the two population best represents the renal progenitors [Anglani et al.2008]. Growing understanding on the repair and regeneration process in organs like kidney with low cell turn over [Rookmaker et al. 2004] induced us to hypothesize that during repair and regeneration, the terminally differentiated cells of the kidney may exhibit phenotypic flexibility and function as stem cells. In vital organs like kidney, it would be imperative to consider that organ repair would follow a more pragmatic way; where-in somatic cells would acquire phenotypic flexibility rather than activating the quiescent resident stem cell population [Kiefer, 2008].

It is well established that kidney tubular epithelial cells, respond to injury by de-differentiating into mesenchymal phenotype thus recapitulating the processes active during early nephrogenesis [Anglani et al. 2008]. Furthermore, a recent report suggests that regeneration by surviving tubular epithelial cells is the predominant mechanism of repair in ischemic kidneys [Humphreys et al 2008]. Interestingly, the response of glomerular cells to injury is reported to be more complex, involving considerable phenotypic adaptations [Johnson et al. 1994].
Glomerular parietal epithelial cells (GPECs), lining the inner aspect of Bowman’s capsule is known to respond to injury by de-differentiating into embryonic phenotype, similar to that of myofibroblasts with de novo expression of α-SMA [Ng et al. 1999]. Under normal physiological conditions, GPECs are known to migrate and differentiate into glomerular podocytes [Appel et al. 2009]. Moreover, reports suggest that CD133+CD24+ cell subset of PEC of adult human kidney have stem cell properties and participates in renal repair [Sagriniati et al. 2006]. Reparative responses in differentiated glomerular epithelial cells thus represent an injury-dependent regression from adult phenotype to embryonic mesenchymal phenotype [El-Nahas. 2003]. It is suggested that such phenotypic alterations are primarily conceived by glomerular epithelial-mesenchymal trans-differentiation (GEMT) [Bariety et al. 2003].

However, in certain conditions, these changes are also associated with excessive production of ECM resulting in crescent formation and irreversible renal fibrosis [Yee yung et al. 2009].

It is intriguing that renal pathology is caught in this vicious cycle where normal pathophysiological responses to tissue injury such as EMT and fibrosis, can also result in chronic injury culminating in organ failure. Understanding the mechanism of cellular de-differentiation in key glomerular subsets like GPECs would further our knowledge of its role in tissue repair, disease progression and enable more effective targeted therapies for acute and chronic kidney diseases.

Another remarkable regenerative mechanism exhibited by the kidney is the compensatory renal growth after unilateral nephrectomy. This adaptive growth occurs with an increase in the size of nephrons resulting from both hypertrophy and hyperplasia of the renal cellular components [Olivetti et al. 1977]. The role of resident progenitors in the compensatory renal growth is not fully understood in mammals, but stem cells have been identified in lower vertebrates like Elasmobranchs which actively participate in renal growth after unilateral nephrectomy [Elger et al. 2003]. After unilateral nephrectomy, the remaining kidney increases in size and restores normal kidney function within short time period. Although compensatory renal growth is largely referred to as compensatory
hypertrophy, the exact mechanism of this adaptive compensatory growth is not known. Unilateral nephrectomy of the adult animal results in compensatory renal growth but does not involve formation new nephrons [Douglas-Denton et al. 2002]. Studies on the regenerative mechanisms manifesting in adult mammalian kidney would enable us to better understand the processes of repair and regeneration in the kidney which would further enable us to devise better targeted therapies for chronic renal diseases.

*With this rationale the present study is designed to serve the following objectives:*

- To identify, isolate and characterize renal resident stem cells from adult murine kidney.
- To evaluate the progenitor profile of putative kidney stem cells with special reference to its functional staminality by in vitro as well as in vivo nephron development assays.
- To study the mechanism of compensatory adaptive growth of contra-lateral kidney following unilateral nephrectomy in murine model.