

Cellular senescence inhibits renal regeneration after injury with senolytic treatment promoting repair

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Introduction

The ability of the kidney to regenerate successfully after injury is lost with advancing age, chronic kidney disease and after irradiation. The factors responsible for this reduced regenerative capacity and the increased propensity towards fibrosis remain incompletely understood.

This study addressed the hypothesis that the presence of chronically senescent renal epithelial cells generated in response to ageing and kidney disease drives fibrosis and impairs the renal regenerative response after subsequent acute renal injury.

Materials and Methods

Analysis was undertaken on published transcriptomic datasets and staining was performed on anonymised human renal biopsies at Edinburgh Royal Infirmary. In vitro studies were undertaken in human proximal renal tubular epithelial cells (PTECs), using 10Gy gamma-irradiation to induce senescence. In vivo studies compared baseline structure, function and injury responses in young, young-irradiated and naturally-aged 2 year old mice after ischaemia reperfusion injury (IRI) to the kidney. Administration of the Bcl2/w/xL inhibitor ABT-263 which has been shown to selectively deplete senescent cells was used in vitro and in vivo to test its selectivity in senescent vs healthy PTECs in vitro and its safety and efficacy in in vivo studies.

Results

Consistent with the hypothesis, studies of human renal disease demonstrated that senescence biomarkers CDKN1A and CDKN2A rose significantly in kidney disease at a transcriptomic level (Fig A-B). Staining for p21cip1 protein produced by CDKN1A demonstrated significant elevation in human renal biopsies from patients with impaired kidney function (Fig C). In vitro and in vivo studies showed that senescent renal epithelial cells generated in response to irradiation and with physiological aging produce multiple senescence-associated secreted factors including TGFβ1 (Fig D-H). Senescent epithelial cells displayed highly selective sensitivity to the effects of ABT-263 (Fig G). In vivo studies (Fig I-M) showed that animals with increased numbers of senescent cells developed augmented fibrosis and reduced tubular proliferative capacity after injury. Treatment with the Bcl2/w/xL inhibitor ABT-263 reduced senescent cell number and restored a 'young' regenerative phenotype to kidneys, reducing fibrosis, increasing healthy kidney weight and reducing markers of senescence in aged and young-irradiated mice exposed to further injury (Aged: Fig N-R, Young-Irradiated: Fig S-V).

Conclusions

Senescent cells are key determinants of renal regenerative capacity and represent important emerging treatment targets to protect aging and vulnerable kidneys in man.