

Allografts, Immunosuppression and Autophagy: A Conspiracy to Fibrose?**Brain, J.G.**; Thompson, E.; Burt, A.D.; Kirby, J.A.

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Classic chronic ductopaenic rejection has all but disappeared from clinical practice in the last 20 years. There has also been a decline in the incidence of acute rejection, but with the emergence of other pathologies, notably chronic rejection in the absence of ductopaenia. While this can be viewed as a triumph there is little information on the optimum protocols for immunosuppression in liver allograft recipients. Evidence points to patients with recurrent HCV, classed as tolerant and receiving rapamycin having worse outcomes, with increased graft fibrosis. HCV and rapamycin are both known to effect the cellular process of autophagy; which has been shown to prevent cell death due to acetaminophen toxicity and the prevention of senescence in biliary epithelial cells (BEC). To establish whether early features of senescence were present in acute rejection, 35 biopsies of orthotopic liver allografts with biopsy proven acute cellular rejection were analysed by immunohistochemistry. There was significant correlation between the senescence marker p21WAF1/Cip and the BANFF grade ($p=0.034$). Application of oxidative stress to BEC in vitro showed a similar upregulation in p21 ($p<0.01$) with adoption of a senescent morphology. PCR and immunofluorescence analysis of BEC showed static TGF- β 1 and increased TGF- β 2 expression, confirmed by ELISA ($P=0.001$). Oxidative stress, FK506 and Rapamycin revealed increased levels of autophagy ($p<0.05$). Rapamycin and oxidative stress, but not FK506, increased β 6 integrin levels on BEC. Pharmacological inhibition of TGF- β R or autophagy; or peptide blockade of β 6 integrin activity prevented in vitro TGF- β activity. These findings indicate that pleiotropic effects of immunosuppressive agents may play a key role in determining graft outcome. The ability of rapamycin to induce integrin dependent TGF- β signalling may explain its relationship to graft fibrosis.