Thesis Abstract:
Crescentic Glomerulonephritis: Associations and Transforming Growth Factors

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Abstract of a Thesis awarded for the Degree of Doctor of Philosophy
University of Otago, New Zealand 2003

The initial aim of this project was to study the role of mast cells in anti-glomerular basement membrane antibody (anti-GBM) induced crescentic glomerulonephritis (CGN), using experimental autologous, and accelerated autologous rabbit models. A method of biopsy was developed to allow sequential sampling of the kidneys over time, and reduce the number of rabbits required for study.

Early in the project, a significant influx of tissue eosinophilic cells were noted during the progression of the disease, and coincided with the onset of the autologous phase. The study of eosinophil in CGN became the major focus of the project, and early results led to the hypothesis that eosinophils have a relationship GN, and that they may have an association with the fibrotic process by producing certain cytokines such as transforming growth factor (TGF-α) and beta (TGF-β), both of these cytokines being demonstrated by other workers as having direct roles in several scaring and sclerotic conditions.

Using biochemical techniques, light microscopy, transmission electron microscopy, and immunohistochemistry, the eosinophilic cells were confirmed as true eosinophils, and not rabbit heterophil (neutrophil) which has similar morphological features to the eosinophil.

Qualitative and quantitative assessment demonstrated that tissue eosinophils did occur at the onset of the autologous phase, and that they first appeared at, and around, the glomerular vascular pole region. As the glomerular crescents developed, the eosinophils were observed both within the crescents (intracrescentic), and in the interstitium circumscribing the crescent (pericrescentic). Eosinophils were very scant and insignificant in control groups.

The number of eosinophils observed with each individual crescent was associated with the degree of pathological change of the diseased glomerulus, the influx of macrophages, the deposition of collagen within crescents, and glomerular area. An increase in the number of macrophages was also seen in the heterologous phase of the autologous models, preceding the influx of eosinophils at the onset of the autologous phase.

The accelerated autologous model has many similar morphological features to rapidly progressive CGN observed in human renal biopsies, and an audit of human cases was undertaken. The intracrescentic and pericrescentic distribution of eosinophils in human CGN was similar to that observed in the rabbit autologous model. There was also a significant association of eosinophil score with the deposition...
of collagen within crescents.

Eosinophils in approximately one third of human biopsies were positive for TGF-α and TGF-β1 proteins. A sequential expression of the two cytokines by red blood cells and fibrin was also seen. The nuclei of some crescentic fibroblasts showed positive TGF-β1 protein expression.

The results of combined experimental animal research and audited human renal biopsies show significant associations between tissue eosinophils, fibrosis of glomerular crescents, and TGF-α and TGF-β1 proteins. These findings indicate avenues towards further study, and potential pathways for therapeutic intervention. Important considerations are also raised regarding prior research with experimental anti-GBM antibody CGN in rabbits, in which eosinophils may have been 'neglected', but could influence research outcomes in the pathogenesis of this animal model of such a debilitating human disease.

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(Manuscript received 11.09.2003)

View This Item Online: https://www.biodiversitylibrary.org/item/175622
DOI: https://doi.org/10.5962/p.361514
Permalink: https://www.biodiversitylibrary.org/partpdf/361514

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