

Glomerular mesangial cells (MC) ingest human neutrophils (PMN) undergoing apoptosis

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PMN and their toxic contents can injure tissue in glomerulonephritis (GN), but little is known of mechanisms by which PMN are cleared from glomeruli. We have shown that *in vitro* and in the inflamed joint and lung, macrophages ingest intact senescent PMNs undergoing apoptosis or “programmed cell death”, a specific disposal mechanism which appears likely to limit the toxic potential of the PMN.

MC have been observed to ingest apoptotic cells *in vivo*. We now report data which suggest a hitherto unrecognised role for MC in clearance of intact senescent PMN undergoing apoptosis. Human PMN were “aged” for 24 h so as to undergo apoptosis, and incubated for 3 h with adherent MC (passage 4-6, prepared and phenotyped by standard methods). MC appeared to ingest aged PMN, identified by positive staining for myeloperoxidase (MPO). Phagocytosis was confirmed by EM, and quantified by microscopy of MPO-stained cytopreps of a single-cell suspension of MC prepared by trypsinization: $31.5 \pm 1.3\%$ (mean \pm SE, n=22) of MC contained aged PMN. There was minimal uptake of freshly isolated (non-apoptotic) PMN, and dependence of MC uptake of PMN upon apoptosis was also demonstrated by centrifugal elutriation of aged PMN populations to yield fraction with varying apoptosis: the % of MC taking up any one fraction of aged PMN was closely correlated to %PMN apoptosis ($r=0.96$, $P<0.0001$, n=37).

Commentary by John Feehally

I spent much of the 1980's thinking about glomerular disease from the point of view of initiating events - in my case how IgA deposits in the mesangium in IgAN and why sometimes but not always it will provoke progressive inflammation and scarring.

But it never occurred to me to ask the 'big question' which John Savill and colleagues asked which provoked a whole new way of thinking about glomerular injury. We all knew that post-infectious GN despite the intensity of the acute endocapillary inflammation has the happy knack of resolving completely often leaving those who presented with acute nephritic syndrome with little or no residual injury. But we never asked with real curiosity – why? how?

It was in attempting to answer that 'big question' that this abstract introduced us to a realm of inflammatory biology of entire novelty to the renal world. It turned out that the death of inflammatory cells was not always the disastrous event allowing the dead cell to have the final say by spewing its cocktail of cytoplasmic proteases and other injurious molecules into its microenvironment. Instead there was an alternative, programmed cell death ['apoptosis'] ensuring death without mischief. The concept of necrosis and apoptosis as mirror image events which enable the body to control inflammation much better than we ever imagined, was so new to us then, but is now a self-evident truth – the stuff of first year medical student lectures on disease mechanisms.

But for all of us at the time, this was new business indeed, remarkably interesting at a mechanistic level, and also because it provided us some insight into the right answer to the 'big question' which should have concerned all of us who look after patients with post-infectious GN. How could this acute insult get so much better and leave so little legacy compared to the fulminant inflammatory glomerular insults, for example as in pauci-immune focal segmental necrotising GN, or in lupus nephritis.

And at the same time, the mesangial cell began to demand our attention. Not just some sort of 'supporting cell' which keeps glomerular capillary loops open by providing a scaffold, and modifies intraglomerular haemodynamics by its contractility, it also turns out the mesangial cell can 'eat and kill' and provide a glomerulus with a chance of survival rather than destruction.

This abstract was the beginning of a new world of glomerular pathobiology – a true 'paradigm shifter' if every there was one.