P455

P455 -Th17 Cells: A Source of a Pathogenic Circulating Factor?

Dr Carl May[1], Mrs Sarah Hunter[1], Miss Musleeha Chesor[1], Dr Lauren Schewitz-Bowers[2], Dr Phillipa Lait[2], Dr Richard Lee[2], Dr Gavin Welsh[1], Professor Moin Saleem[1]
[1]Bristol Renal, Bristol, United Kingdom, [2]Inflammation and Immunotherapy, University of Bristol, Bristol, United Kingdom

The identity of the pathogenic circulating factor in Nephrotic Syndrome has been the subject of intense research. Several candidates have been postulated and refuted through the years. Much circumstantial evidence points towards factor(s) released by T cells, though a specific T cell phenotype has not been identified.
A steroid resistant population of Th17 cells have been postulated as key effector cells in in conditions such as autoimmune uveitis. We hypothesised that Th17 cells could also be important drivers of immune mediated nephrotic syndrome.
Th17 cell culture supernatant was applied to human conditionally immortalised podocytes in vitro. Western blots confirmed that there is indeed cross-talk between these two cell types. Both JNK and p38 MAPK pathways were stimulated by Th17 cell culture supernatant treatment. Downstream of JNK, Paxillin was also phosphorylated. These signalling events are associated with an increase in cellular motility. Accordingly, scratch assays of podocytes treated with Th17 cell culture supernatant demonstrated a significant increase in motility, which could be attenuated by inhibition of JNK. Individual cytokines (IL-17, IL-23, IL-6, IL-1b) at the concentrations present in the supernatant had no effect on podocyte motility. This is clear evidence that Th17 cells are capable of signalling to the podocytes and eliciting a behavioural response.
Work carried out previously in the lab has demonstrated a clear role for the PAR-1 receptor in the pathogenesis of nephrotic syndrome. Intriguingly, PAR-1 agonist treated podocytes show activation of the same intracellular signalling pathways as the Th17 cell culture supernatant treated podocytes. A concomitant increase in motility was also observed.
Importantly, PAR-1 inhibition is capable of blocking the podocyte's response to Th17 supernatant treatment.
Taken together this work indicates that Th17 cells are potentially a source of a Podocyte Damage Factor and that this unknown factor could be working via the PAR-1 receptor. Both the Th17 cells themselves and the PAR-1 receptor are therapeutic targets and also present a route to specifically identify the factor.