Neutrophils are a major component of innate immunity and indispensable for host defence against invading pathogens [1]. Due to their tissue destructive ability, neutrophils are also intimately associated with the development of acute inflammatory disorders such as ARDS and myocardial infarction. Traditionally, neutrophils have been considered as short-lived “kamakazi” cells that arrive rapidly at sites of infection and injury, are over-exuberant in their activity, and die within the infiltrated tissue. Growing body of evidence has however challenged this dogma suggesting that neutrophils may have a longer life-span than previously considered (e.g. 5.4 days in humans) [2], can be detected in lymphoid organs [3], are associated with the pathogenesis of numerous chronic inflammatory disorders and exhibit elaborate interactions with components of the adaptive immune response [4]. Emerging evidence also indicates the presence of different neutrophil sub-sets with distinct phenotypic and functional profiles in various disease scenarios [5]. Furthermore, contrary to being dead-end cells, neutrophils can exhibit reverse transmigration [6-8], a phenomenon that recent studies stemming from our laboratory has associated with development of systemic inflammation [9] (see below and (Figure 1)). Collectively, current evidence indicates a broader role for neutrophils in inflammation, immunity and pathogenesis of inflammatory disorders than conventionally considered, emphasising the need for greater insight into the mode, mechanisms and implications of neutrophil trafficking in vivo.

In this regard, using an advanced confocal intravital microscopy platform, we have analysed details of neutrophil-vessel wall interactions in real-time in 3D and have noted previously unreported physiological responses (e.g. sub-endothelial cell crawling [10]) and also potential pathological events such as “disrupted” modes of neutrophil transendothelial cell migration (TEM) [9]. The latter includes the first direct observation of in vivo neutrophil reverse TEM (rTEM) within a mammalian system. In investigating the pathophysiological relevance of this event, we noted that neutrophil reverse TEM was most prevalent following ischemia-reperfusion (I-R) injury and was associated with the presence of a subset of functionally primed neutrophils within the pulmonary vasculature which correlated with the development of acute lung inflammation [9]. These results suggest that neutrophils that have undergone reverse TEM have a distinct and activated phenotype, and as a result, may contribute to turning a local inflammatory response into a systemic multi-organ phenomenon (Figure 1). As the above findings have identified a potentially new paradigm in dissemination of systemic inflammation, and since there is evidence

![Figure 1](image-url)

**Figure 1** Proposed model for how neutrophils stemming from a primary site of tissue/vascular injury (i.e. reverse transmigrate back into the circulation) may contribute to the development of second organ (e.g. lung, kidney) injury
for occurrence of human neutrophil reverse TEM [8], our work is currently addressing the hypothesis that primed neutrophils can migrate out of inflamed tissues back into the circulation and drive inflammation at a distant site, a phenomena that has important implications for numerous human pathologies including possibly vasculitis. Collectively, whilst it has long been known that inappropriate, excessive or prolonged leukocyte transmigration is associated with the pathogenesis of inflammatory disorders, despite much research there has been a disappointingly slow progress in fruitful targeting of leukocyte trafficking for development of anti-inflammatory drugs, indicating a need for better understanding of the intricacies of targeted pathways. With this in mind and considering the revitalised interest in the role of neutrophils in both acute and chronic inflammatory disorders [11], there is a need for better understanding of the mode and mechanisms of neutrophil-vessel wall interactions in vivo. Furthermore, despite the colossal advancements in genomics and proteomics, the underlying cause of many common disorders is unknown and will likely be advanced through rigorous analysis of cellular behaviours. Hence, questions such as the potential role of neutrophil reverse transendothelial cell migration in development of second organ injury will be of fundamental importance. Most notably as systemic inflammation is a common and life-threatening adverse outcome of many clinical conditions (e.g. trauma, ischemia-reperfusion injury, vasculitis), this response with unknown aetiology requires further investigations. Overall, our studies have demonstrated that detailed analysis of neutrophil-vessel wall dynamics are likely to identify novel and disease-specific phenomena that could promote a change in thinking towards development of new therapeutic strategies.

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L3. Are mononuclear cells predominant actors of endothelial damage in vasculitis?

Introduction

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) constitute a group of disorders characterized by autoimmune necrotizing inflammation of small blood vessels, which leads to systemic organ damage [1]. This group of systemic vasculitides includes granulomatosis with polyangiitis (PGA), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS). These disorders are predominantly associated with the presence of circulating ANCA that are directed against proteins in cytoplasmic granules of neutrophils. ANCA with specificity for proteinase-3 (PR3-ANCA) are associated particularly with GPA, whereas ANCA with specificity for myeloperoxidase (MPO-ANCA) are predominant in MPA and to a lesser degree in CSS [2]. Although it remains unknown how these conditions develop, it has been postulated that ANCA in vivo bind to surface expressed autoantigens (PR3 or