Immune-mediated lung disease

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It’s all immune...?

• Diseases that doesn’t have immune involvement?

• The processes of response to injury and tissue repair are key homeostatic pathways involved in all tissues throughout life.
AF’s presentation

• Arrives at A&E. One month of mild malaise and cough, now fairly sudden onset of fever.

• Coughing small amounts of blood.

• Temperature 38 C, RR 25, SaO2 94%, p110, Urea 8, BP 110/70

• Neutrophils raised, CRP 250 (normal <10)
AF’s management

- Diagnosed with pneumonia
- Blood cultures, sputum cultures, broad spectrum antibiotics (co-amoxiclav and clarithromycin)
- CURB-65 score = 1 (3.2% mortality)
- Looks pretty poorly, kept in
Axel’s progression

• Deteriorates over next few days
• More haemoptysis
• Increasing breathlessness, sats worsening, CRP fails to respond, antibiotics changed, but renal function deteriorates
• A diagnostic test was performed…
ANCA-associated vasculitis

- Main types include microscopic polyangiitis (MPA, usually p-ANCA MPO), granulomatosis with polyangiitis (GPA usually c-ANCA PR3), eosinophilic granulomatosis with polyangiitis (EGPA p-ANCA).

- There are older names for some of these that have fallen out of favour.
Autoantibodies to neutrophil proteins

- Not clear how these arise: molecular mimicry? Failed neutrophil clearance?
- Staph aureus may have some overlapping peptide sequences, and there are some HLA associations
Mechanisms

Figure 1

(A) Extracellular events induced by the binding of ANCA to neutrophil plasma membrane. ANCA is capable of binding both antigen via its F(ab′)2 fragments and FcγR via its Fc region. This interaction leads to an activation of the cell with release of mediators such as pro-inflammatory cytokines, superoxide and granule components.

(B) Intracellular events induced by the binding of ANCA to neutrophil plasma membrane. ANCA binding initiates a dual signalling cascade which involves activation of G-protein-coupled pathways by F(ab′)2 ligation and tyrosine-kinase-coupled pathways by Fc ligation. These pathways involve a number of other molecules and converge in order to produce a functional response.

(C) ANCA instigates neutrophil adhesion to endothelial cells and transmigration. Binding of ANCA to the plasma membrane of neutrophils leads to their progression from rolling along the endothelial surface to firm adhesion. The production of chemotactic factors by the endothelial cells induces transmigration of the neutrophils into the subendothelial space and their resultant production of reactive oxygen species and release of proteolytic enzymes generates vascular damage.

Fewer studies have taken place to determine the role of the monocytes/macrophages in development and progression of SVV. Monocytes are capable of expressing both PR3 and MPO and are therefore a legitimate target for ANCA. The cells are seen within granulomas and glomerular crescents during active disease and so, by implication, play a part. Monocytes are able to release reactive oxygen species, cytokines/chemokines [MCP-1 (monocyte chemotactic protein-1), IL-8, TNFα, IL-1β and IL-12] and thromboxane in response to ANCA and consequently may contribute to the local pro-inflammatory environment [10]. Furthermore, ANCA-treated monocytes can up-regulate the surface adhesion molecules CD14 and CD18 [83] and down-regulate CD62L, giving rise to increased adhesion.

In vitro vascular modelling and release of PR3 Binding of ANCA to neutrophils induces their adhesion to cytokine-activated endothelial cells [64], in vivo this would trap them at vessel walls. If concurrently the neutrophil releases superoxide and then undergoes accelerated apoptosis without clearance (leading to secondary lysis and release of toxic intracellular contents), then bystander injury can occur. The release, particularly of PR3, has been shown to have wide-ranging effects on endothelial cells [84] leading ultimately to their apoptosis, but also provoking the production of IL-8 and MCP-1 and the increased surface expression of ICAM-1 and VCAM-1, all pro-inflammatory events.

The adhesion of ANCA-treated neutrophils to cytokine-treated endothelial cells has been modelled in vitro under physiological flow conditions which mimic the shear stresses seen within vessels (Figure 1C). The experiments have demonstrated both the importance of cytokines in the system plus the role of various adhesion molecules and chemokines. Endothelial cells treated with high concentrations of TNFα are capable of capturing neutrophils flowing past and transmigration occurs. If the endothelial cells receive only low doses of TNFα then cells roll but do not adhere firmly. If, however, the neutrophils are pretreated with ANCA then adhesion proceeds and the neutrophils transmigrate. For these events to ensue, β2 integrin engagement is necessary and our group has demonstrated [84a] that CD11a/CD18 and CD11b/CD18 both play a role, with CD11b probably being more important in promoting stable adhesion. There is also a role for chemokine receptors in this process with CXCR2 (CXC chemokine receptor 2) blockade being able to decrease the response.

B-cells Evidence both from the animal model of Xiao et al. [18] and from patient studies [14] have implicated ANCA-IgG and, therefore, B-cells in ANCA-associated

Williams et al 2005
Mechanisms

- Recruitment of activated neutrophils, production of ROS and neutrophil degranulation
- Generation of microabscesses, recruitment of monocytes and macrophages, lymphocytes to make granulomas
- Devastating inflammation affecting many organs, including lung and kidney
Treatment

• Immunosuppression: steroids and cyclophosphamide

• Plasma exchange

• Maintenance with rituximab* or other immunosuppressants.

• * An anti-B cell drug. It probably reduces B cells producing ANCA, but likely has other mechanisms too.
More RA complications
Progressive disease
RA and the lungs

- **Pleural effusions**
  - Exudates, metabolically active, low glucose.

- **Fibrosing alveolitis**
  - Relatively treatment-resistant.

- **Airways disorders**
  - Bronchiolitis, bronchiectasis, obliterative bronchiolitis; reasonably common.
And there’s more

• **Drug toxicity**
  • Relatively rare with MTX, increasing concerns with leflunomide.

• **Complications of immunosuppression**
  • PCP well-described, TB reactivation with anti-TNF.

• **Pulmonary hypertension**
  • Described occasionally.

• **Other complications of connective tissue disease**
  • Myositis
And more

- **Organising Pneumonia**
  - Steroid-responsive patchy consolidation/focal disease.

- **Nodules**
  - Uncommon, usually in association with nodules elsewhere. Typically peripheral. Cavitation described. Colonisation of existing cavities with mycobacteria or Aspergillus described.

- **Vasculitis**
  - An important pulmonary complication of RA and connective tissue diseases that can present with large areas of focal disease with or without cavitation.
Guillain-Barre Syndrome

- Antecedent infection such as Campylobacter, influenza or CMV
- Acute inflammatory demyelinating polyneuropathy secondary to anti-myelin antibodies
- Treatment: plasma exchange or IVIG*
- *Yes, you’ve guessed it, we don’t know how it works
Problems of immunity

• Innate and adaptive immunity

• Innate immunity: humoral components, activation of neutrophils and macrophages, anti-viral defence

• Adaptive immunity: formation of antibodies, activation of B and T cell immunity
Mechanisms of immune-mediated damage

- Bystander damage: tissue damage in chronic infection
- Excessive immune response
- Failure to control immune like responses
- On-target immune response
- Off-target immune response
Bystander damage

• An infection won’t clear, e.g. because of non-immune defects in cystic fibrosis.

• Chronic neutrophil recruitment results in persistent cellular activation, release of proinflammatory mediators and tissue damage.

• Perhaps seen in COPD, where chronic neutrophil recruitment, B cell activation, macrophage activation all occur
Excessive immune response

• **Without antibodies:** ARDS: neutrophilic, innate immune activation

• **With antibodies:**
  
  • Asthma: atopic disease related to responses to harmless aeroallergens
  
  • EAA: type III/IV hypersensitivity with reactions to organic dusts
Failure to control natural immune activation

- Alpha-1 anti-trypsin disease: emphysema
On-target immune responses

• Bronchiolitis obliterans of your own (GvHD) or someone else’s (lung transplant) airways.

• A useful part of treatment (GvL), but side effects of immune damage to the airways

• Distinguish from immunosuppression and chronic infection (mess with the immune system at your peril)

• Treatment: GvHD = steroids, lung transplant BOS less clear (azithromycin?)
Off-target immune responses

- AAV
- Goodpasture’s syndrome: antibodies to type IV collagens after some viral infections
Immunity gone wrong

- Not completely clear what the mechanisms are, except the immune and repair systems are activated

- Connective tissue associated ILDs, inc organising pneumonia and other complications of RA.
Other places immunity plays roles

- Responses to cancer and its control, metastasis
- Cardiovascular disease in association with lung disease: acute and chronic risks
- Systemic features of diseases such as COPD
Clever targeting

• The increasingly molecular age of medicine allows individual targeting of cytokines:

• Anti-IL-6 in RA, Anti-IL-5 in asthma.
Conclusions

- Immunity, as in the activation of inflammation and repair mechanisms, underpins many or most of the pathological responses of respiratory diseases.

- As always, appreciation of mechanism can guide treatment, but treatments often to date relatively non-specific.