Inflammation in the clinic

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The immune system acts in four general ways to ensure host defence

- Exclusion barrier
- Identification of “non self”/Tolerance of “self”
- Elimination
- Memory
A breakdown or dysfunction in one or more of these activities can lead to inappropriate immune responses including the inflammatory component.
as well as being involved in host defence, the immune system is also involved in disease and adverse outcome in some situations

- **Autoimmune** – response to self antigen
- **Allergic** – response to benign environmental or food antigen
- **Inflammatory bowel disease** – response to commensal bacteria
- **Low grade chronic inflammation** – response to local injury
- **Overzealous inflammatory response** – adverse outcome from surgery, injury, trauma, critical illness
Dendritic cells sample the environment and initiate inflammation via T cell activation.
The five cardinal clinical signs of inflammation
Inflammatory cell recruitment into tissues and their activation for release of chemical mediators

- Rolling
- Adhesion
- Diapedesis

**BLOODSTREAM**
- Systemic effects (including inflammation)

**TISSUE**
- Chemoattractants
- Inflammatory cytokines
- Vasoactive mediators

- Inflammatory cytokines
- Inflammatory eicosanoids
- Reactive species

- Activated leukocytes

**Th2**
T lymphocytes are the orchestrators of the inflammatory response

Holgate ST. Innate and adaptive immune responses in asthma. Nat Med 2012: 18; 673-83
Data from US Centre for Disease Control

The influence of the changing environment: diet, chemical and pollutant exposure, reduced biodiversity in microorganisms (microbiome)

Inverse relationship between the incidence of prototypical infectious diseases and the incidence of immune disorders

Inflammation – a ticking time bomb
The report considers inflammation in several clinical settings

- **Metabolic conditions**
  - Obesity, Type-2 diabetes, Cardiovascular disease
- **Autoimmune/Immune mediated inflammatory diseases**
  - Rheumatoid arthritis, Crohn’s disease, Psoriasis
- **Allergic diseases**
  - Asthma, atopic dermatitis, food allergy
- **Neurodegenerative disease**
  - Alzheimer’s
Rheumatoid arthritis
Immunopathological features of rheumatoid arthritis

- Synovial and systemic inflammation (increased blood TNF$\alpha$, IL-6 and CRP)
- Damage to cartilage and bone in and around joints -> destruction & loss of function
- Synovial lining cells – macrophage-like & fibroblast-like
- Cellular infiltration of synovial membrane (macrophages - TNF, IL-1, IL-6)
- Synovial fibroblasts - metalloproteases and prostanoids
- T cells involved (increased T cell cytokines in joints and in circulation: IFN-$\gamma$, IL-17)
- Fewer regulatory T cells and bias towards mediator-secreting Th1/Th17 cells
- B cells produce autoantibodies (e.g. rheumatoid factor – not RA specific though)
- TNF and IL-6 blocking antibodies work well in RA
Chronic Mucosal Inflammatory Disorders

Crohn’s Disease

Ulcerative Colitis

Rhinosinusitis

Asthma

When You Have Asthma
Crohn’s Disease (regional enteritis): terminal ileum, colon and usually effects young people

Also cause complications outside the gastrointestinal tract such as skin rashes, arthritis, inflammation of the eye, tiredness, and lack of concentration.
Crohn’s Disease (regional enteritis)

- GI tract mucosal and systemic inflammation (increased blood TNF, IL-6 and CRP)
- Damage to GI tract mucosa (crypt abscesses)
- Heavy inflammatory cell infiltrate (macrophages - TNFα, IL-1, IL-6)
- T cells involved (increased T cell cytokines in gut mucosa and in circulation: IFN-γ, IL-17)
- Fewer regulatory T cells and bias towards Th1/Th17 cells
- Anti-microbial antibodies (breakdown in mucosal “barrier”); some autoantibodies
- Usually responds to anti-TNF and against the cellular adhesion molecule α4-integrin blocking antibodies
Psoriasis
Psoriasis

- Hyperproliferation of keratinocytes & abnormal angiogenesis of the skin
- Skin microbes involved
- Skin lesions
- Inflammatory cell infiltrate (T cells - bias towards Th1/Th17 with increased IFN-γ and IL-17)
- Interaction with skin dendritic cells
- Systemic inflammation (increased blood TNF, IL-6 and CRP)
- Comorbidity: IBD, arthritis, ankylosing spondylitis

Brodalumab, an Anti–Interleukin-17–Receptor Antibody for Psoriasis
Asthma

Strongly associated with allergic comorbidities – rhinitis, conjunctivitis, eczema and food allergy
Asthma

- Airways dysfunction in response to allergens or irritants (obstruction, mucous formation, oedema, inflammation - poor lung function and inability to breathe)

- Airways remodelling - scar tissue and increase in smooth muscle - poorly responsive

- Inflammatory cell infiltrate (eosinophils, other granulocytes, mast cells, T cells -> bias towards Th2 with increased IL-3, IL-4, IL-5, IL-9, GM-CSF and IL-13, eosinophil granule proteins, cysteinyll leukotrienes, PGD₂)

- Systemic inflammation (increased blood IgE and Th2 cytokines)
Biologics targeting Th2 cytokines and chemokines

Holgate ST Nature Rev Immunol 2009
Atopic dermatitis

Primary defect in epithelial permeability: Filaggrin mutations
Atopic Dermatitis (eczema)

- Skin irritation and lesions in response to allergens or irritants
- Often other co-morbidities (e.g. asthma, food allergy)
- Skin lesions
- Inflammatory cell infiltrate (eosinophils, mast cells, T cells – Th1 + bias towards Th2 with increased IL-4, IL-5 and IL-13)
- Systemic inflammation (increased blood IgE, Th2 cytokines)
- Deficiency in filaggrin, a precursor of skin lubricants involved in keratinocyte barrier function
- Responds to corticosteroids and tacrolimus that interfere with T cell functions
Obesity

Obesity is a complex condition characterized by excess body fat. It can lead to various health issues, including cardiovascular disease, diabetes, and sleep apnea. The diagram illustrates the cycle of obesity, showing how overnutrition leads to increased fat accumulation, which in turn causes inflammation and insulin resistance. This cycle can also affect the liver, leading to liver insulin resistance. The inflammatory signals, such as adipocytokines and pro-inflammatory cytokines, play a crucial role in this process. Understanding these mechanisms can help in developing strategies to combat obesity.
Obesity

- Low-grade systemic inflammation (increased blood TNF, IL-6 and CRP)

- Inflammatory cell infiltrate of adipose tissue (macrophages - TNF, IL-1, IL-6)

- Adipose tissue secretes inflammatory mediators (cytokines, chemokines …)

- The anti-inflammatory mediator adiponectin is DECREASED in obesity whereas other adipokines increase

- Visceral adiposity is more inflammatory than subcutaneous

- T cells involved too

- Inflammatory burden is decreased by weight loss either through bariatric surgery OR lifestyle change
Cardiovascular disease

Atherosclerosis timeline:
- Foam cells
- Fatty streak
- Intermediate lesion
- Atheroma
- Complicated lesion/rupture
- Fibrous plaque

Endothelial dysfunction:
- From first decade
- From third decade
- From fourth decade

Growth mainly by lipid accumulation
- From first decade
- From third decade
- From fourth decade

Thrombosis, hematomas
Smooth muscle and collagen

Coronary artery
Narrowing of the arteries
Plaque rupture & clot formation
Cardiovascular disease

• Low-grade systemic inflammation (increased blood TNF, IL-6 and CRP)

• Inflammatory markers are predictive of future morbidity and mortality

• Endothelial inflammation - upregulated adhesion

• Inflammatory cell infiltrate of vessel wall macrophages/foam cells - TNF, IL-1, IL-6, MMPs

• T cells involved too (Th1 bias)
Neurodegeneration: Alzheimer’s Disease
Common features of inflammatory processes

1. A normal inflammatory response but in the wrong context

2. Inappropriate barrier function (epithelial or endothelial), inappropriate triggering (e.g. loss of tolerance), lack of down regulation (loss of Treg numbers and function), tissue destruction with loss of function

3. Common “pleotropic” mediators: cytokines (TNF, IL-1β, IL-6, IFN-γ), chemokines (IL-8, MCP-1), eicosanoids (PGE₂, 4-series LT), MMPs, ROS

4. Common signalling pathways: STATs, P₃₈ MAP kinase, NFκB, PPAR-γ
Pharmacological targeting of inflammation

Anti-inflammatory drugs have a major influence on disease-related biomarkers

- Focus on airways inflammation
Application of topical corticosteroids to the treatment of asthma

1947: First use of cortisone in RA
Hench PA,
Mayo Clinic

Mean change in lung function

Suppresses inflammation

Inhaled Steroids in Asthma
Optimizing Effects in the Airways

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Corticosteroids

Inflammatory cells
- Eosinophil
  - Numbers (apoptosis)
- T-lymphocyte
- Mast cell
- Macrophage
- Dendritic cell
  - Numbers

Structural cells
- Epithelial cell
  - Cytokines Mediators
- Endothelial cell
  - Leak
- Airway smooth muscle
  - β2-Receptors
  - Cytokines
- Mucus gland
  - Mucus secretion
Corticosteroids

- Inhaled corticosteroids

Epithelial cells

- Cytokines
  - IL-1β
  - IL-6
  - GM-CSF
  - RANTES
  - Eotaxin
  - MIP-1α

- Enzymes
  - iNOS
  - COX-2
  - cPLA₂

- Peptides
  - ET-1

- Adhesion molecules
  - ICAM-1

↓ INFLAMMATION
Effect of corticosteroids on gene transcription

Biologics targeting specific disease pathways is the future: stratified or personalised medicine
Anti-IgE

IL-4, IL-13 → IgE

B lymphocyte

FcεRI

Mast cell

Histamine, Cys-LTs, PGD₂

FcεRII (CD23)

Macrophage

Chronic inflammation

Anti-IgE omalizumab

T lymphocyte

Eosinophil
Screening
Lead Development
Candidate Selection
Clinical Trials: Phase I  Phase II  Phase III/IV  Novel therapeutic

Improved animal models and target validation

Better understanding of disease and unmet need
Targeted patient populations
Improved smaller & faster clinical trials
Targeted effective and safe medicines

Understanding patient’s responses

‘omic technologies (phenome)
Informatics (integration)
Patient phenotyping
Application
Research diagnostics  ➔ Commercial diagnostics

£££ €€€ $$