Intestinal immunology

Spier Paediatric Gastroenterology 2019
Basic Immunology 101
A brief refresher

Slides from Frank lecture series on Immunology (Youtube)
Innate Immunity

- Inflammation
- Phagocytosis
- The Complement System
- Interferons
- Infected cell
- Effector NK cell
- NK Cells
Innate Immune System

PAMPs → PRRs

Recognized by

TLR, CLR, NLR, RLR

Plasma membrane

Nucleus

cytosol

endosome
Adaptive Immunity

AQUIRED IMMUNITY

Major Components are:
- Antigen Presenting Cells (APCs)
- B-Cells
- T-Cells

Adaptive Immunity

Specific Immunity

Immunological Memory is Present

Slower but long-lasting immune response
Immunocompetence occurs in different sites

- B cells complete maturation in Bone marrow
- Pre-T cells move to Thymus - complete maturation in thymus
Major Histocompatibility Complex (MHC)

- MHC genes
- MHC molecules

Class I
- Expressed on all nucleated cells

Class II
- Expressed on Antigen Presenting Cells
Co-receptors: CD4 and CD8
T Cell Activation and Differentiation: CD8⁺ Cells

- T cell
- Proliferation
- Differentiation
- CD8⁺ Effector T Cells
- CD8⁺ Memory T Cells

Active CD8⁺ T cell
Cytotoxic T cells contain specific cytotoxic granules

- Perforin forms pores in the membrane of target cell
- Granzymes cause apoptosis or programmed cell death
- Granulysin has antimicrobial activity
Intestinal immune system: GALT
Challenges of the Intestinal Mucosa

• Large surface area (300m²)
• Exposure to:
  • Microbes (10^{12} micro-organisms/g stool)
  • Ingested antigens (30kg food protein/year)
• Digest and absorb food, water & electrolytes
• Single layer epithelium
• Rich blood supply and lymphatic network

BUT

• Must keep pathogens out
• Avoid excessive immune response to food antigens and microbes
Features of the Intestinal Immune Response at Rest

• Immune suppressed

• Tolerance to food antigens (local & systemic)

• Tolerance to commensal organisms (local, not systemic)
Organisation of the Intestinal Immune System

First Line of Defence

- Microbiome
- Mucus
  - Goblet cells
- IEC and tight junctions
- IgA
- Antimicrobial Substances
  - Paneth cells
Anatomy of Intestinal Immune System
Response to Antigens
Transport across the epithelium to Dendritic Cells
B-cells
Production of secretory IgA

Secretory IgA

- Maintains mucosal barrier
- Less pro-inflammatory than other Ig’s
- Protects against infection
- Oral tolerance
T Cells

Pro-inflammatory

Suppressive/ less inflammatory
T Regulatory Cells
Mechanisms of Action

• Cytokine mediated effects (TGF-β, IL-10, IL-35)

• Direct cytolysis of APC & effector cells

• Metabolic disruption/direct inhibition of DC maturation

Julia Bollrath, Fiona M. Powrie. Seminars in Immunology. 2013
Balance between proinflammatory & tolerant Ag response

• Pro inflammatory
  • Th 1
  • Th 17

• Tolerant
  • Th 2
  • TReg

Ruemelle 2013
Immune Balance in the Intestine

- Absence of Treg
- Enhanced immune reactivity
- Barrier disruption
- Decreased immune reactivity

References:
Oral Tolerance

Specific suppression of cellular/humoral immune response to an Ag by prior administration of the Ag by the oral route

Normal tolerance cannot be established in the absence of a gut flora
Mechanisms of Tolerance

- Epithelium integrity
- sIgA
- Tolerogenic DC’s
- Treg cells
  - TGF beta
  - IL10
- Macrophages – IL10 release
Intestinal diseases

Immunodeficiency or dysregulation
IPEX syndrome
IPEX

• Immune dysfunction, Polyendocrinopathy, Enteropathy, X-linked
• Presents first months of life
• Intractable diarrhoea, FTT, eczema
• Diabetes mellitus, hypothyroidism

• Mutations in FOXP3 gene
Coeliac Disease
Coeliac disease

• Immune-mediated systemic disorder elicited by ingestion of wheat protein gliadin

• T-cell mediated, chronic inflammatory disorder with an autoimmune component

• Genetically predisposed - gliadin activates innate and adaptive immune system

• Predominantly TH1
There are a range of possible HLA-DQ protein types, from DQ1 to DQ9, that are located on the surface of cells to act as receptors of antigen molecules.

HLA-DQ2 and HLA-DQ8 bind gluten peptide fragment more strongly and can trigger an immune response more easily.
Inflammatory bowel disease

• Dysregulation of the normally controlled immune response to commensal bacteria in a genetically susceptible individual

• Genome-wide association studies: Crohn’s disease – alterations in gene coding for NOD2 – innate immune system

• Mutations in ATG16L1 – genes involved in degradation of intracellular pathogens, antigen processing, regulation of cell signalling and T-cell homeostasis

• Altered recognition and processing of bacterial antigens may play a role in disease pathogenesis
Intestinal immunity and diet
Vitamin A
Vitamin A

- Reduces all cause mortality < 5 years
  - Diarrhoeal disease
  - Measles
- Prophylactic supplementation reduces severity of diarrhoea
Vitamin A in the Intestine

Vitamin A regulates gene expression

Marc Veldhoen and Verena Brucklacher-Waldert, 2012
Mucosal Immune Effects of Vitamin A

- Favours Treg differentiation (together with TGF beta)
- CCR9 and α4β7 integrin expression
- Promotes Th2 cell differentiation
- Opposes Th17 cell differentiation (increases TGF beta; decreased IL6)
Mucosal Immune Effects of Vitamin A

• Maintains intestinal epithelial integrity
• Regulates mucin gene expression
• Normal IgA production
• Reduces autoimmunity
Vitamin D

- Control of infection
- Cancer
- Autoimmune disease
- Diabetes
- Osteoarthritis
- Periodontal disease
Vitamin D

- Inhibits Th1/ enhances Th2
- Treg ↑
- TCR expression (but delays TCR-mediated signalling)
- DC maturation ↓
- Decreases secretion: IL-1, IL-6, IL-8, IL-12, IL-17, IL-23 & TNF-α

Marc Veldhoen and Verena Brucklacher-Waldert, 2012
Vitamin D

• ↓Th17 differentiation & homing

• Enhances innate immunity
  • IEL recruitment
  • Stabilises tight junction structures
  • Stimulates expression of NOD2/CARD15/IBD1
  • Paneth cell secretion

Marc Veldhoen and Verena Brucklacher-Waldert, 2012
Conclusions

• Intestinal function is closely linked to immune regulation
• Loss of normal immune regulation leads to a number of intestinal diseases
• Oral tolerance is influenced by dietary factors and the intestinal microbiome
• Future research will define interventions for the treatment of the immune mediated diseases.