2017 CST-Astellas Canadian Transplant Fellows Symposium

Immunology of Transplantation Rejection

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Dr. Jean Tchervenkov is Professor of Surgery at McGill University Health Center in Montreal, Quebec. He is currently the Director of Live Donor Kidney Transplantation Services at the Royal Victoria Hospital and Director of Pediatric Transplantation at the Montreal Children's Hospital. His main research activities include the role of donor specific transfusion in tolerance induction in vascularized solid organ transplantation; donor cell trafficking following donor-specific transfusion and the role of the thymus in allograft tolerance; and the effect of intraportal vein donor-specific transfusion on small bowel and other vascularized allograft survival. Other interests include that of the role of T&B cells in Allo & Xeno rejection. His clinical research is that in immunosuppression of Hepatitis B & C in liver, and kidney expanded criteria donors, and the immunosuppression of kidney transplantation. His work has been supported by several grants received from the Royal Victoria Hospital Research Institute, the Canadian Red Cross Society, the Canadian Association of General Surgeons, and various pharmaceutical companies. Dr. Tchervenkov is a fellow of the Royal College of Physicians and Surgeons of Canada and the American College of Surgeons. He is a member of many professional and Academic organizations including the Canadian Association of General Surgeons, the Canadian Transplant Society, the American Society of Transplant Surgeons, the Transplantation Society, the American Association for the Study of Liver Disease, and the American Hepato-pancreato-biliary Association. Dr. Tchervenkov continues to be competitive by attending scholarly congresses both in Transplantation and Immunology. He has over 100 publications in peer reviewed medical journals and has presented over 150 (oral & poster) abstracts. Dr. Tchervenkov graduated from McGill University, and came on staff at the Royal Victoria Hospital in 1990.

Disclosure

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Organ Transplantation and the Mechanisms of Rejection

- Organ Transplantation is the Ideal Treatment of End Stage Organ Failure
- Potential Benefit restricted due to Organ Availability and Limitations of **Long-term Organ survival.**
- Current half life is between 6-15 yrs (lung to liver)
- Both Non immunological (ischemia reperfusion, disease recurrence) and **Immunological** are the major reasons of graft loss.
- Chronic Allograft Rejection or Antibody Mediated Rejection are the Predominant features of **Immunological** Graft Loss.

Organ Transplantation and the Mechanisms of Rejection -The Immune Response

The Innate (Natural) Immune response

- Made of physical and chemical Barriers (skin,mucosa, mucous secretions etc.), proteins of the complement system, immune cells (macrophages, neutrophils, NK and innate lymphoid cells).
- Characterized by limited germline encoded receptor diversity and responds to pattern recognition receptors (PRRs).
- PRRs respond to Pathogen –associated molecular patterns (PAMPS).
- PRRs include Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin-like receptors(CLRs), and scavenger receptors.

Organ Transplantation and the Mechanisms of Rejection -The Immune Response

The Innate (Natural) Immune response

- PRRs respond to tissue injury released molecules such as heat shock or nuclear proteins and are collectively named damage –associated molecular patterns (DAMPS). DAMPS are also released during allograft rejection.
- PRR binding activates the immune cells of the innate system.
- The Innate system is responsible and is complemented by the more refined Adaptive or Acquired Immune system.

Organ Transplantation and the Mechanisms of Rejection -The Immune Response

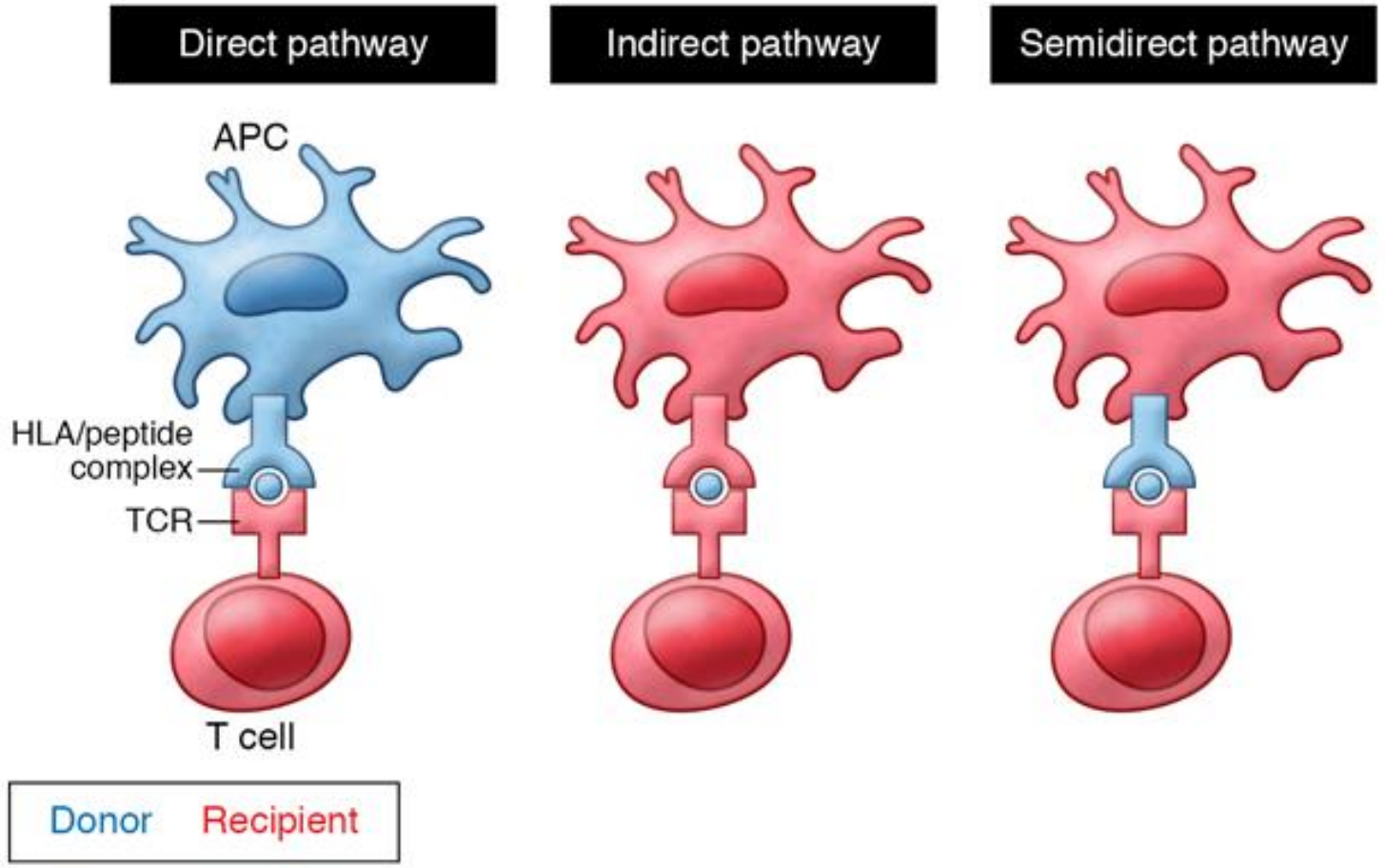
The Adaptive Immune Response

- The T cell compartment – antigen recognition and activation. Effector functions mediated by T cells.
- The B cell compartment- antigen recognition and activation. Effector functions mediated by Bcells.
- Harmful antibodies in solid organ transplantation.

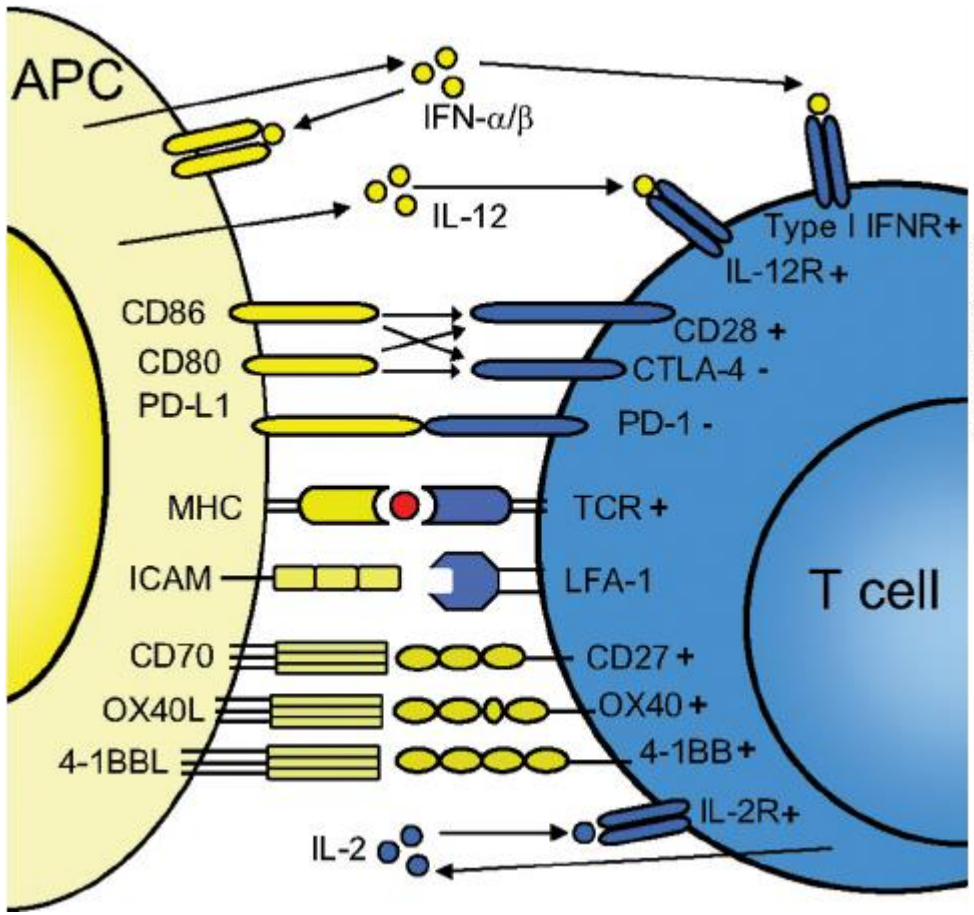
The Tcell Compartment

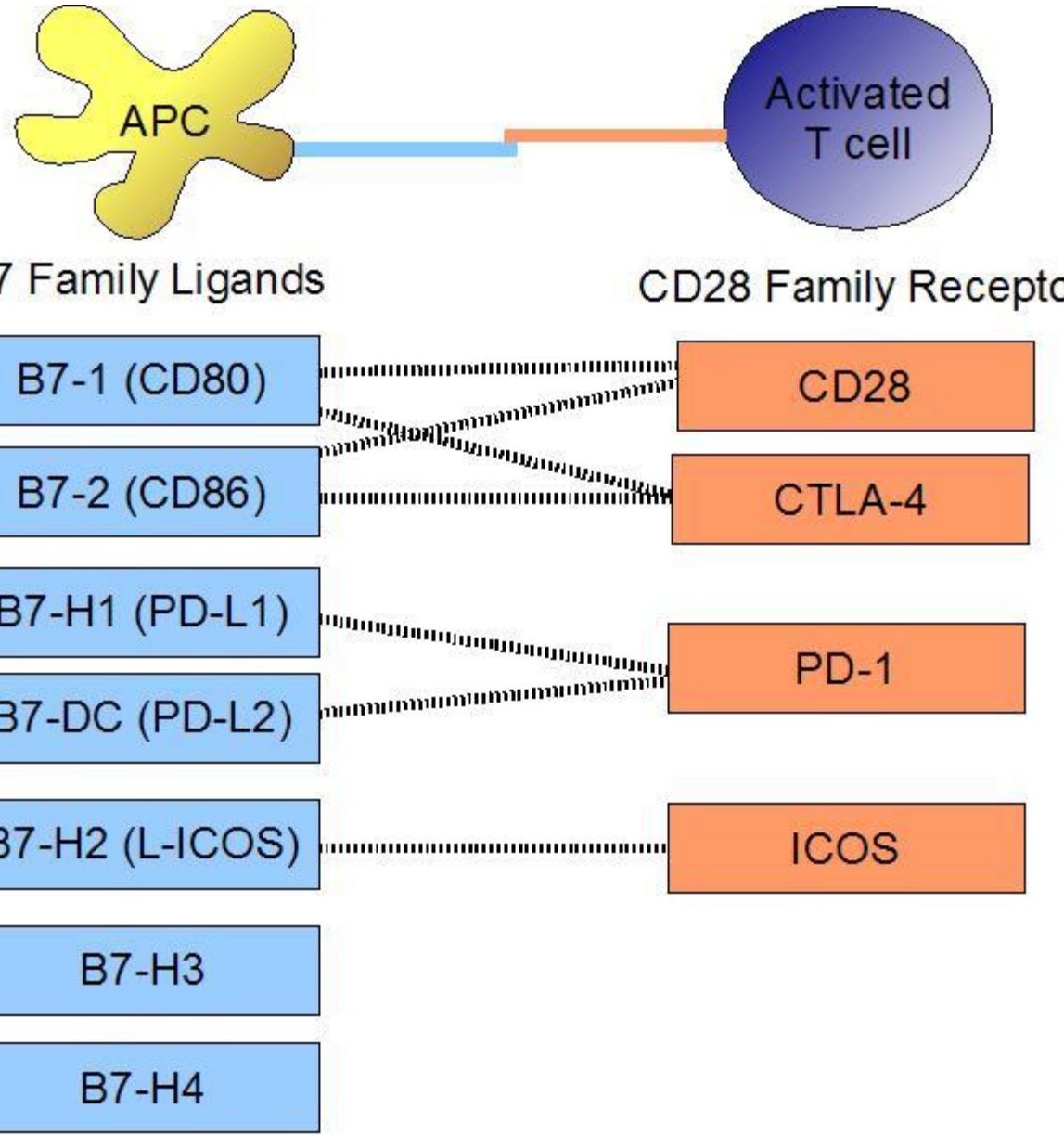
- Dendritic cells or APCs are activated by innate immune system following DAMPS release.
- These Donor APCs migrate to recipient Lymphoid system and present foreign HLA to primed Tcells (CD4, CD8).
- CD4 recognize foreign peptide in the context of Class II MHC and are crucial in the helper functions (Bcell activation and Antibody production and switch).
- CD8 recognize foreign peptide in the context of Class I MHC and are associated with cytotoxic and effector T cell functions.

T cell Activation Pathways in Allograft Rejection

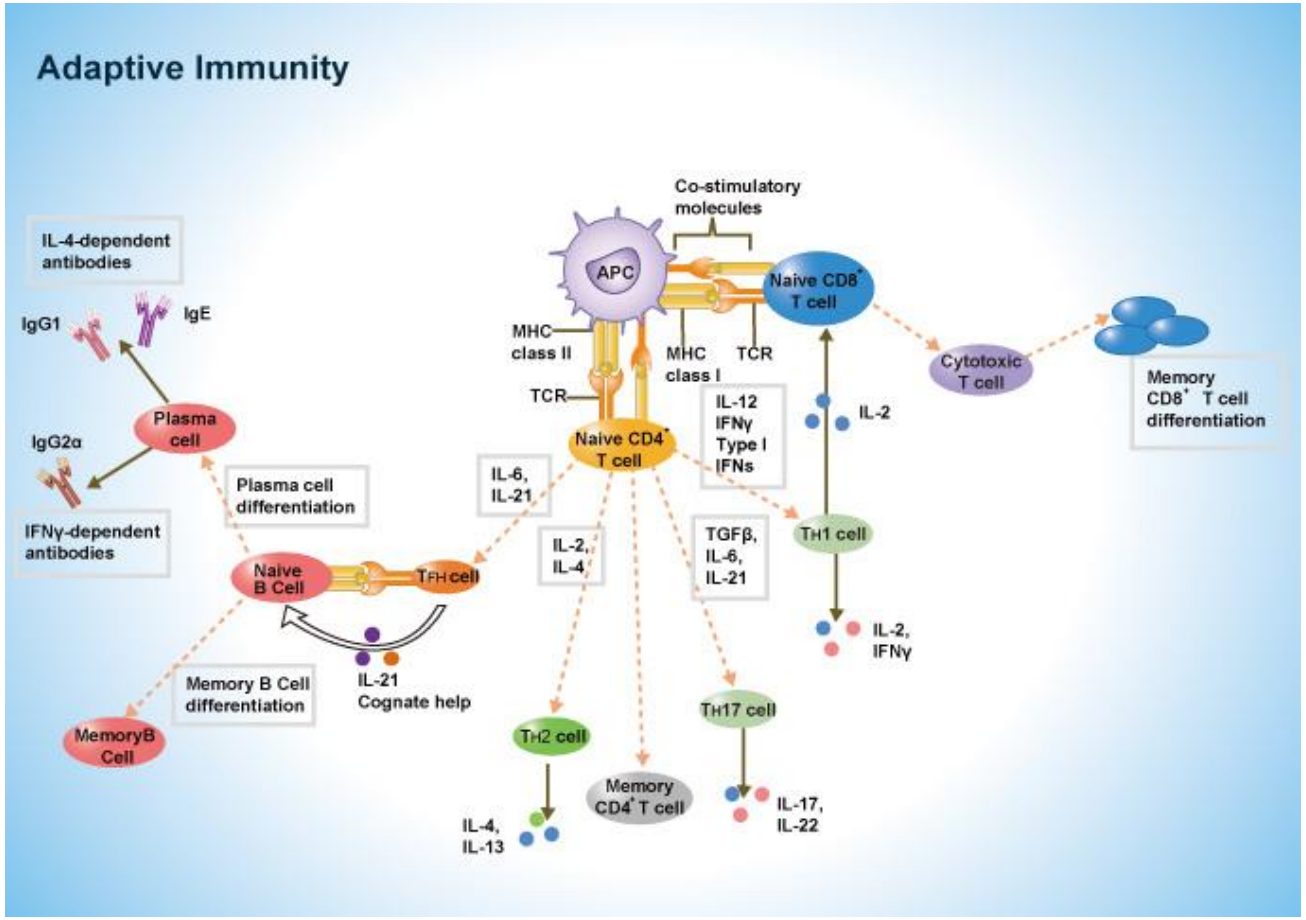


Tcell activation by MHC

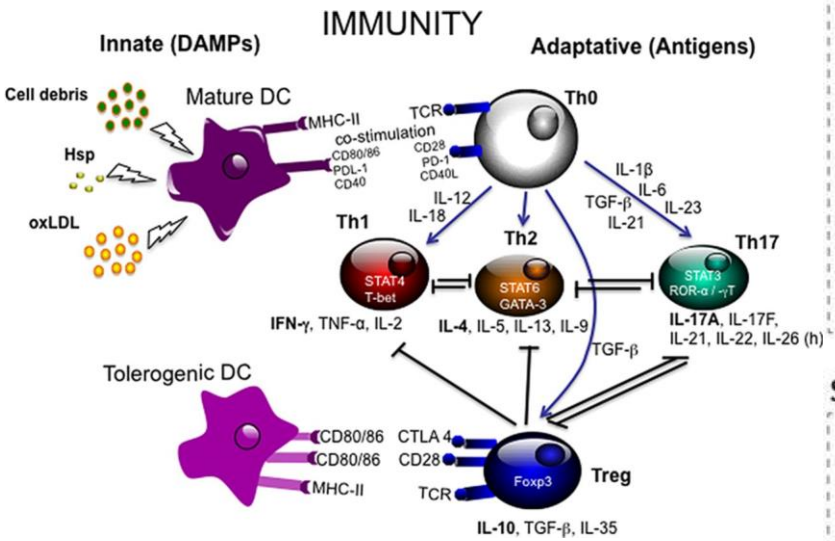


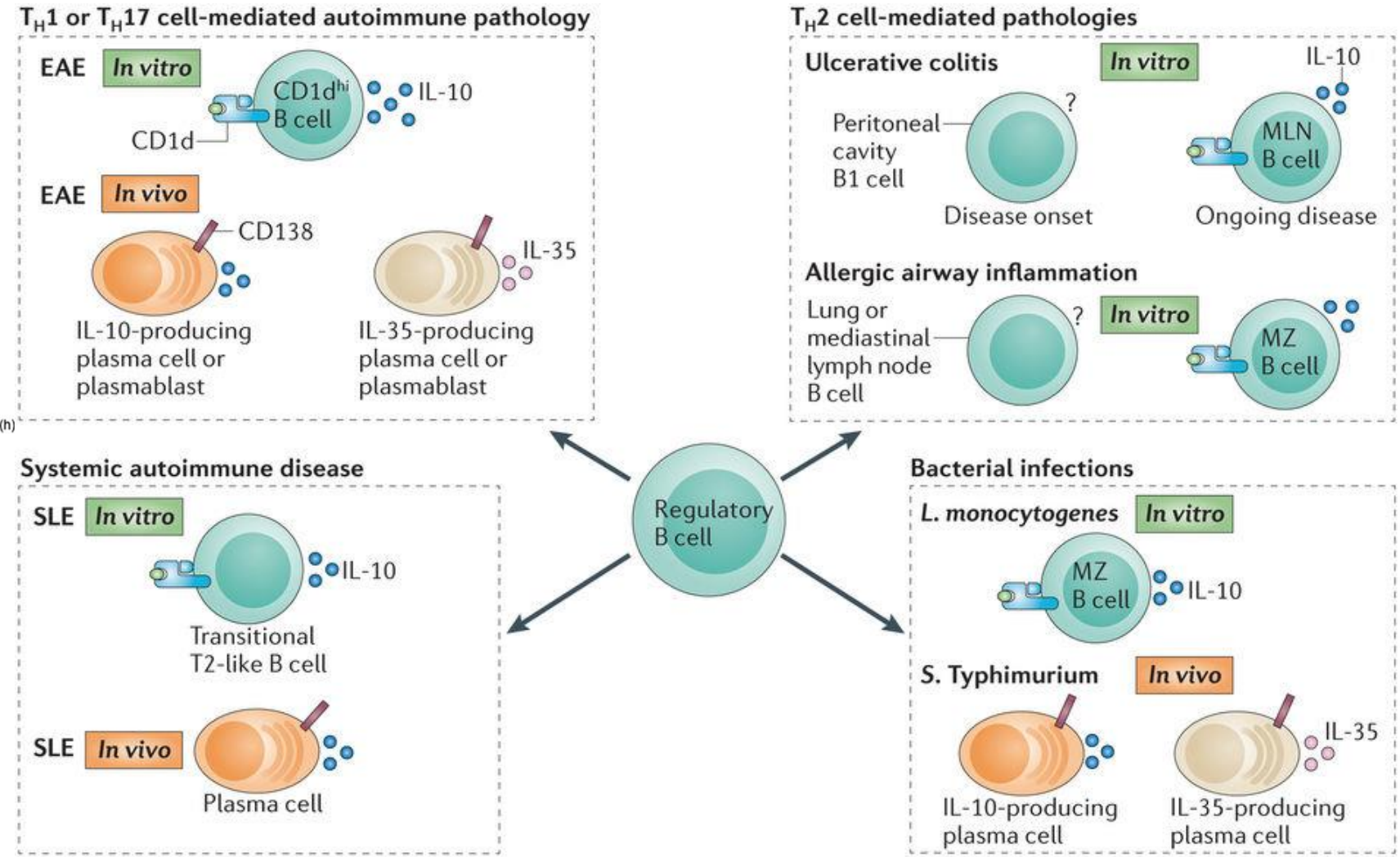


Tcell activation by MHC



Th 17, Treg , DC reg and B reg interaction





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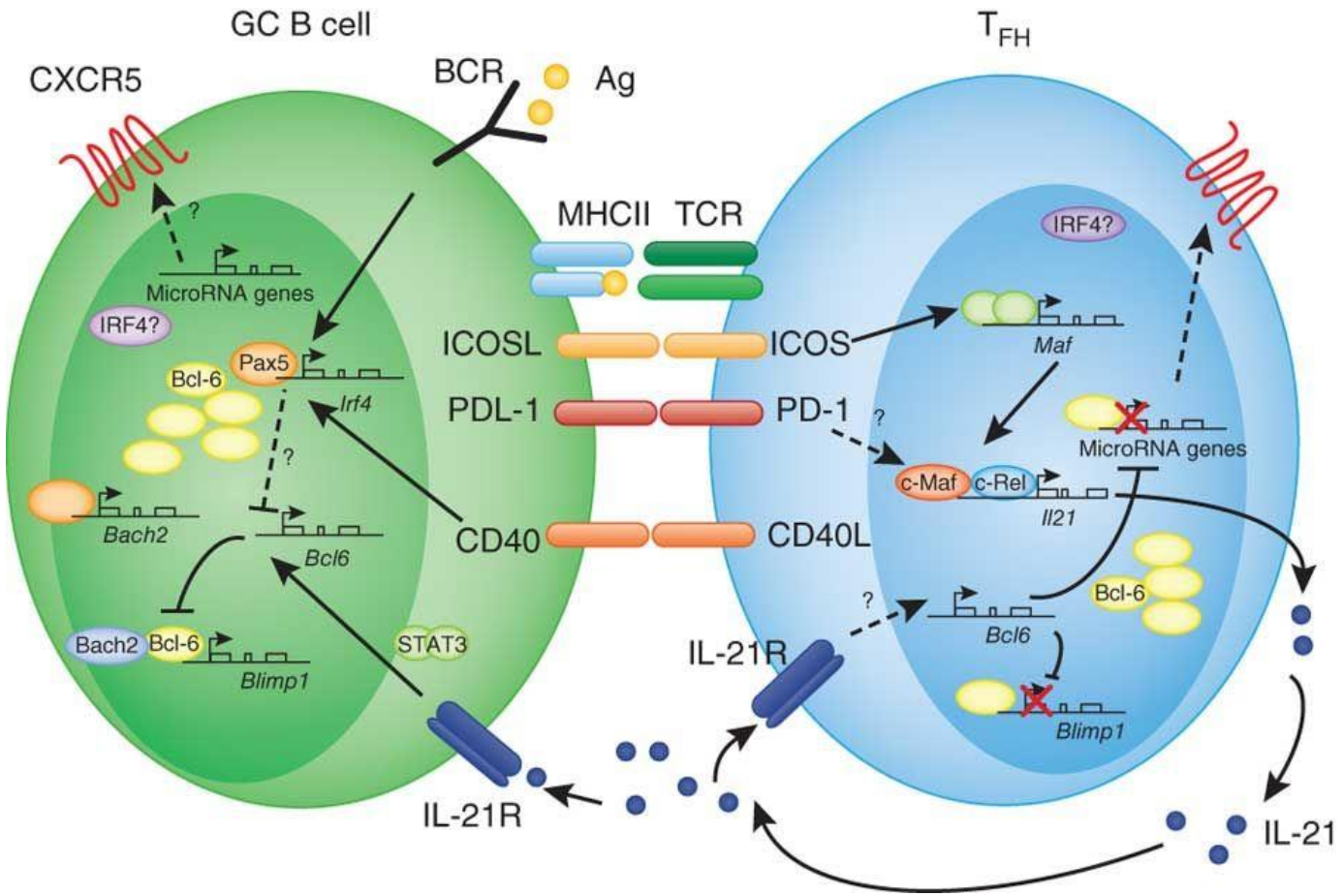
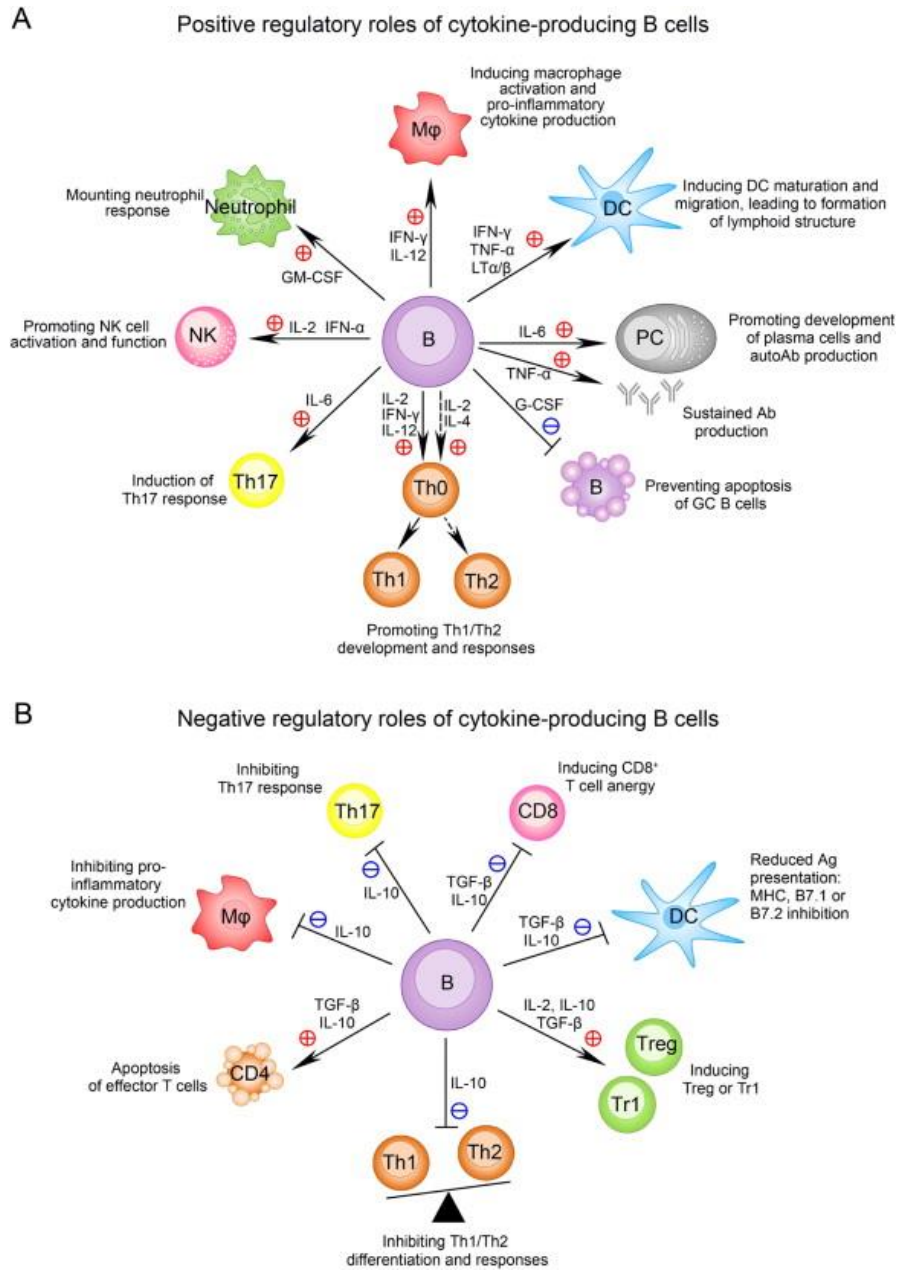
The B cell Compartment

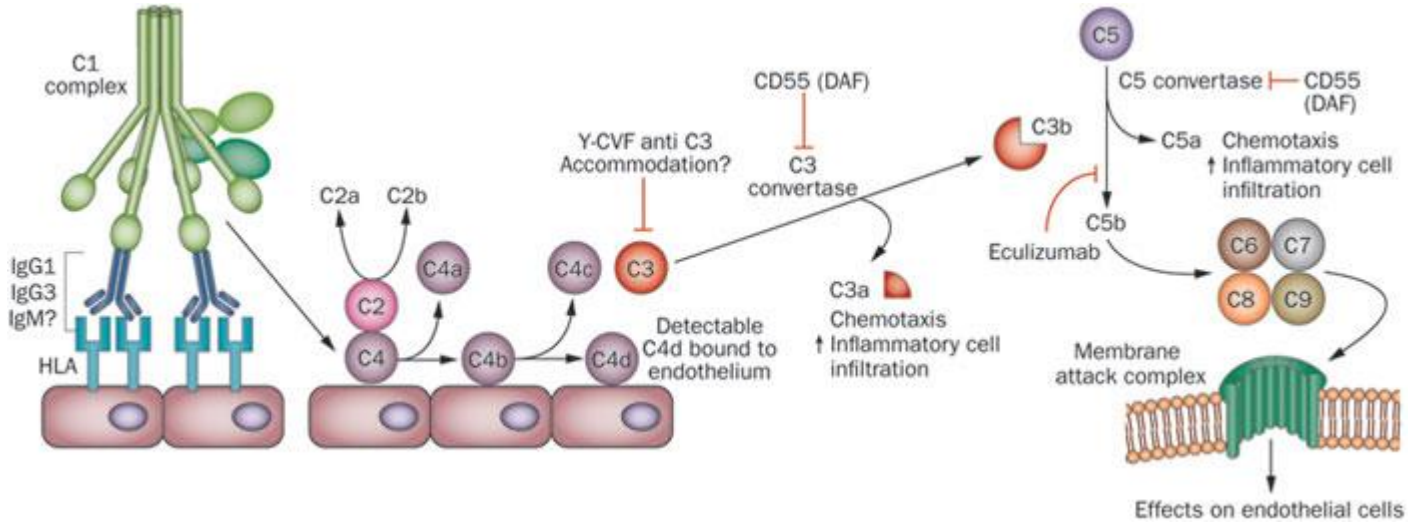
- Unlike the T cell B cells can recognize antigen through their IgD or monomeric IgM. These together with other associated Proteins form the Bcell receptor (BCR).
- However Bcells need CD4+ Tcell help to respond and ultimately class switch to produce antigen specific IgG. Co stimulation CD40-CD40L is required.
- Effector function of B cells is mediated by secreted antibodies (IgG 1 - 4) that are complement binding or complement independent.
- Some Bcells develop into short lived or long-lived plasma cells whilst others will differentiate into **memory B cells**.

B cell and CD4+ Tcell interaction

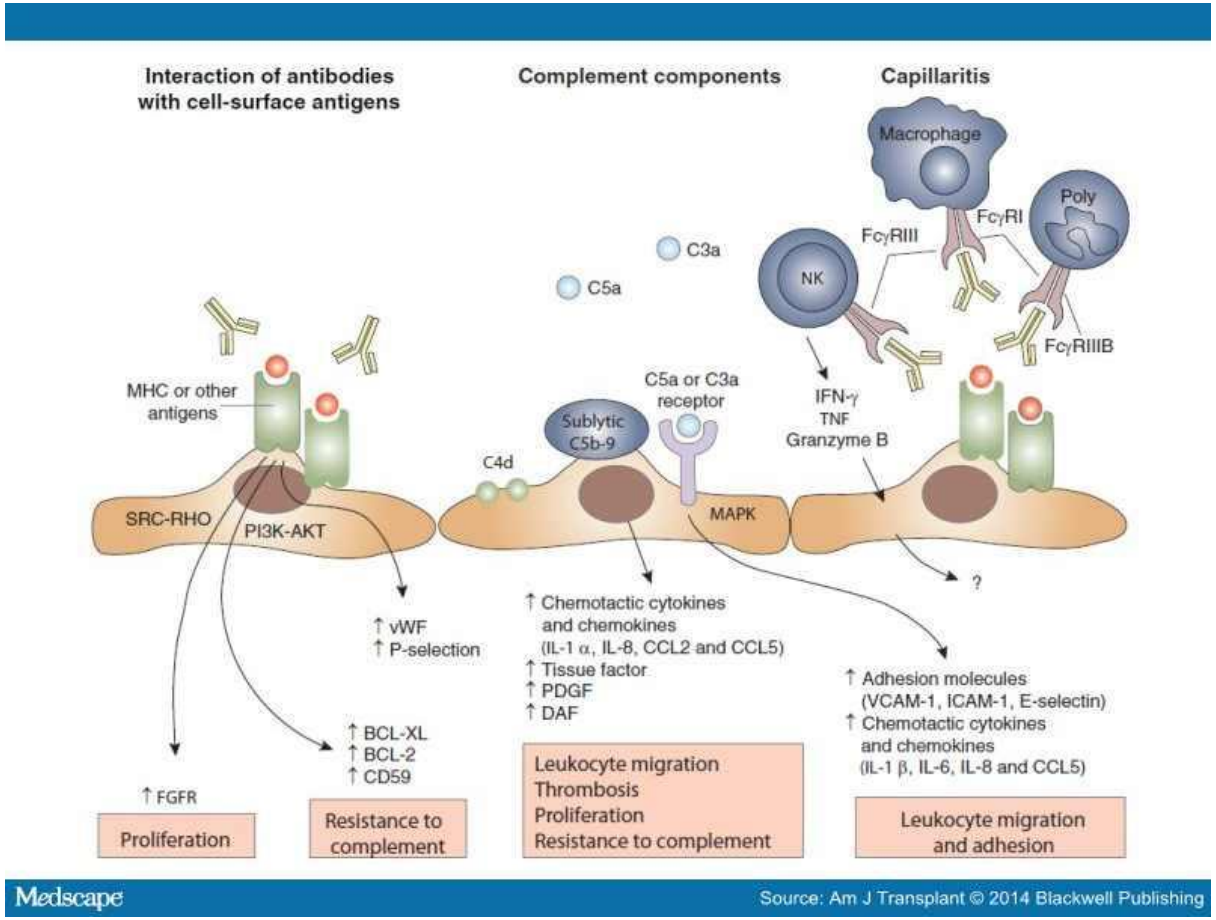



A
Positive regulatory roles of cytokine-producing B cells
Inducing macrophage activation and pro-inflammatory cytokine production
Mφ
Mounting neutrophil response
Neutrophil
GM-CSF
IFN-γ
IL-12
IFN-γ
TNF-α
LTα/β
DC
Inducing DC maturation and migration, leading to formation of lymphoid structure
Promoting NK cell activation and function
NK
IL-2 IFN-α
B
IL-6
PC
Promoting development of plasma cells and autoAb production
TNF-α
Sustained Ab production
IL-6
IL-2
IFN-γ
IL-12
IL-2
IL-4
G-CSF
Induction of Th17 response
Th17
Th0
B
Preventing apoptosis of GC B cells
Th1
Th2
Promoting Th1/Th2 development and responses
B
Negative regulatory roles of cytokine-producing B cells
Inhibiting Th17 response
Th17
Inducing CD8+ T cell anergy
CD8
Inhibiting pro-inflammatory cytokine production
Mφ
IL-10
TGF-β
IL-10
Reduced Ag presentation: MHC, B7.1 or B7.2 inhibition
DC
IL-10
TGF-β
IL-10
B
TGF-β
IL-10
IL-2, IL-10
TGF-β
Apoptosis of effector T cells
CD4
Treg
Tr1
Inducing Treg or Tr1
IL-10
Th1
Th2
Inhibiting Th1/Th2 differentiation and responses

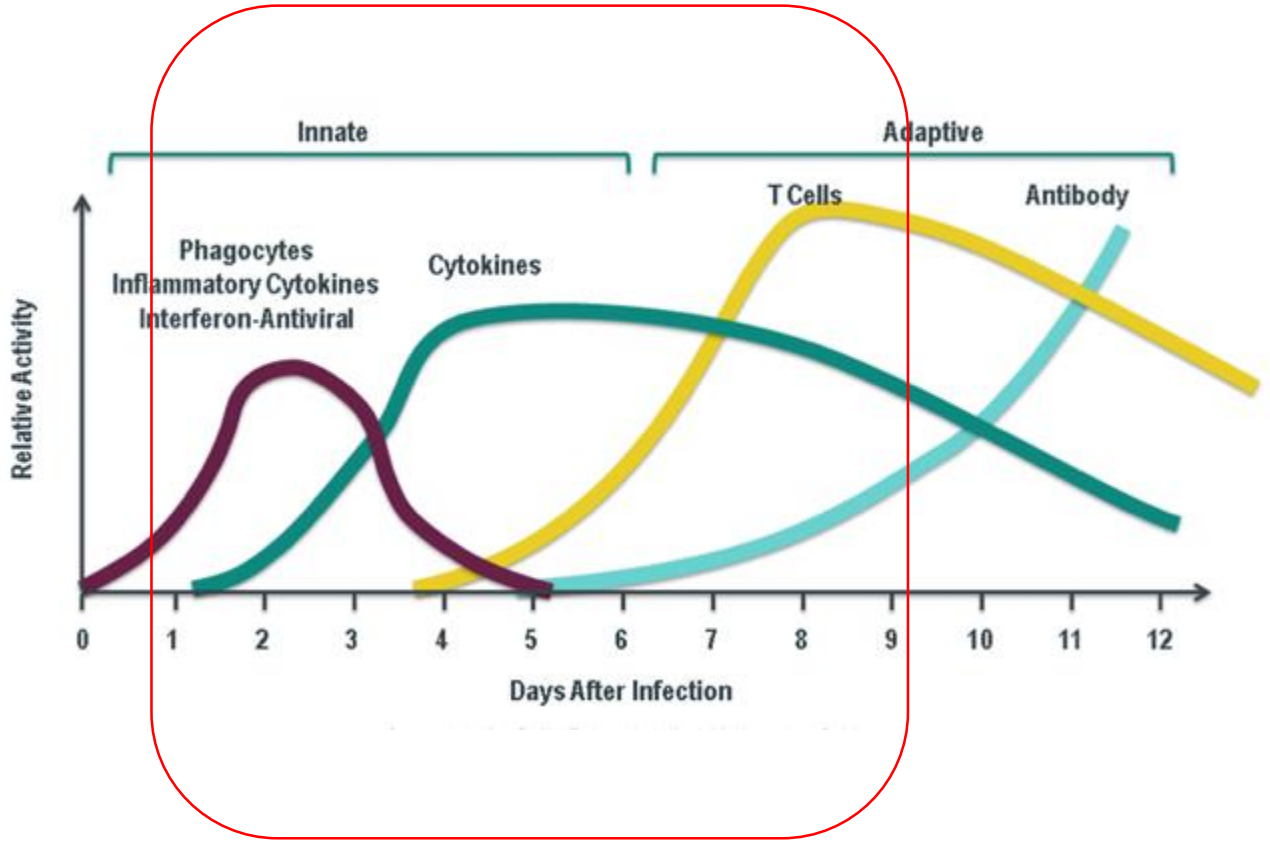
Complement binding of IgG and Antibody Mediated Rejection.



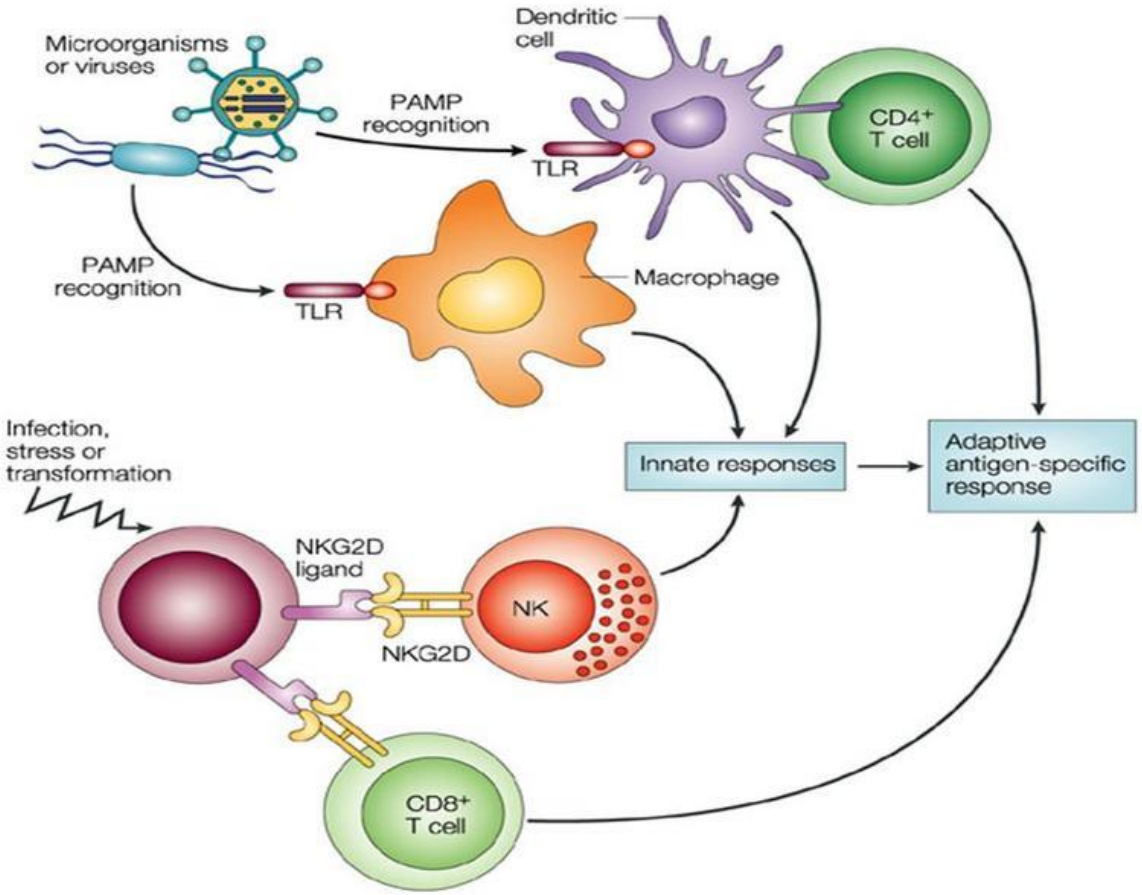
Complement Independent Antibody Mediated Rejection.

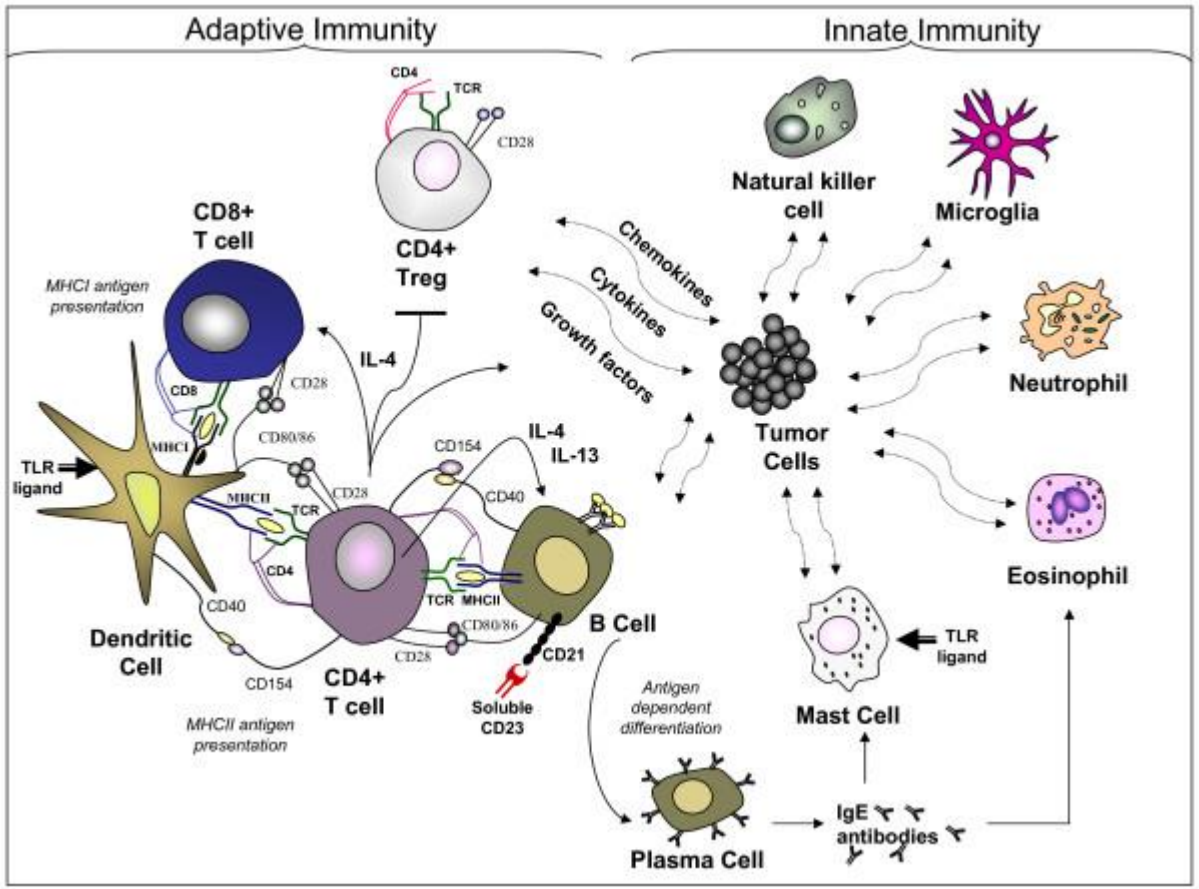


The Immune Response Timeline



The Innate Immune System/ Adaptive Interaction.





Features of AMR in Histopathology of Different Organs

Table 1. The overarching features of AMR for cardiac, renal, pancreas, liver, lung, bowel, and composite tissue allografts

		Features of acute antibody-mediated rejection					
Organ/ Tissue	**Consensus criteria**	**Evidence of HLA DSAs needed**	**Concurrent allograft dysfunction needed**	**C4d**	**Microvascular inflammation**	**Immune cell infiltration**	**Notes**
Heart	Yes (29, 39)	May or may not be present; but consideration to return to criteria (40)	No; may be clinical or subclinical	May or may not be present; linear capillary staining i+[A] if positive	May or may not be present; "EC swelling," dilation, CD31 h+[A] if positive	May or may not be present; intracapillary CD68 macrophages and other IAMCs	Not all are required for a definitive diagnosis
Kidney	Yes (30)	Yes; required (HLA or non-HLA)	No; may be clinical or subclinical	Yes; linear PTC staining	Yes; glomerulitis or peritubular capillaritis	Yes; predominant monocyte component (116)	All are required for a definitive diagnosis
Pancreas	Yes (32)	Yes; required (HLA); "suspicious" if missing	Unknown; in ref. 192, all were for-cause biopsies	Yes; only if in IACs	Acinar injury, cytoplasmic swelling, vacuolization, capillary dilatation	Interacinar capillaritis with mononuclear cells or PMNs; CD68 can be helpful	C4d alone is insufficient but with MVI
Lung	Yes (33)	Yes; required (HLA)	No; may be clinical or subclinical	May or may not be present; alveolar capillary staining only	Not explicitly required; but described in ref. 95, as capillaritis	Neutrophilic capillaritis and arteritis; CD68 not informative	All are required for a definitive diagnosis
Liver	Yes (31); others: refs. 100, 118	Yes; required (HLA)	Unknown; studies report only for-cause biopsies, since protocol biopsy of this organ is rare	Yes; diffuse, >50% portal tract staining microvasculature, with or without sinusoidal or central vein involvement (98, 100)	Yes; portal microvascular endothelial hypertrophy, portal capillary and inlet venule dilatation	Monocytic, eosinophilic, and/or neutrophilic portal microvasculitis; CD68 less informative in this organ	
Intestine	No (193)	Recommended (35)	Unknown; lack of consensus: yes (194), no (195)	Recommended (35)	Possibly; capillary dilatation and congestion (196)	Adherent inflammatory cells in vessels; more severe rejection with transmural inflammation (195, 196)	Not well defined because of nonspecific C4d staining and paucity of vessels in biopsies
Composite tissue	No; early mention in ref. 34, but AMR is not part of these Banff 2007 criteria	Unknown	Unknown; not enough clear evidence	May not be informative (99)	Possibly; vasculitis (34)	Neutrophil margination	

Where consensus criteria have been described, the most recent citation is given. Where consensus criteria have not yet been published (intestine and composite tissue), relevant references describing putative features of AMR in these organs are given. [A]For cardiac transplantation, "pathological" AMR (pAMR) may be diagnosed in the setting of histological evidence of allograft injury (h+), such as capillary endothelial changes, and/or immunopathological evidence of AMR (i+), such as positive C4d staining. EC, endothelial cell; IACs, interacinar capillaries; IAMCs, intracapillary activated mononuclear cells; MVI, microvascular inflammation; PMN, polymorphonuclear cells, such as neutrophils; PTC, proximal tubule cell.

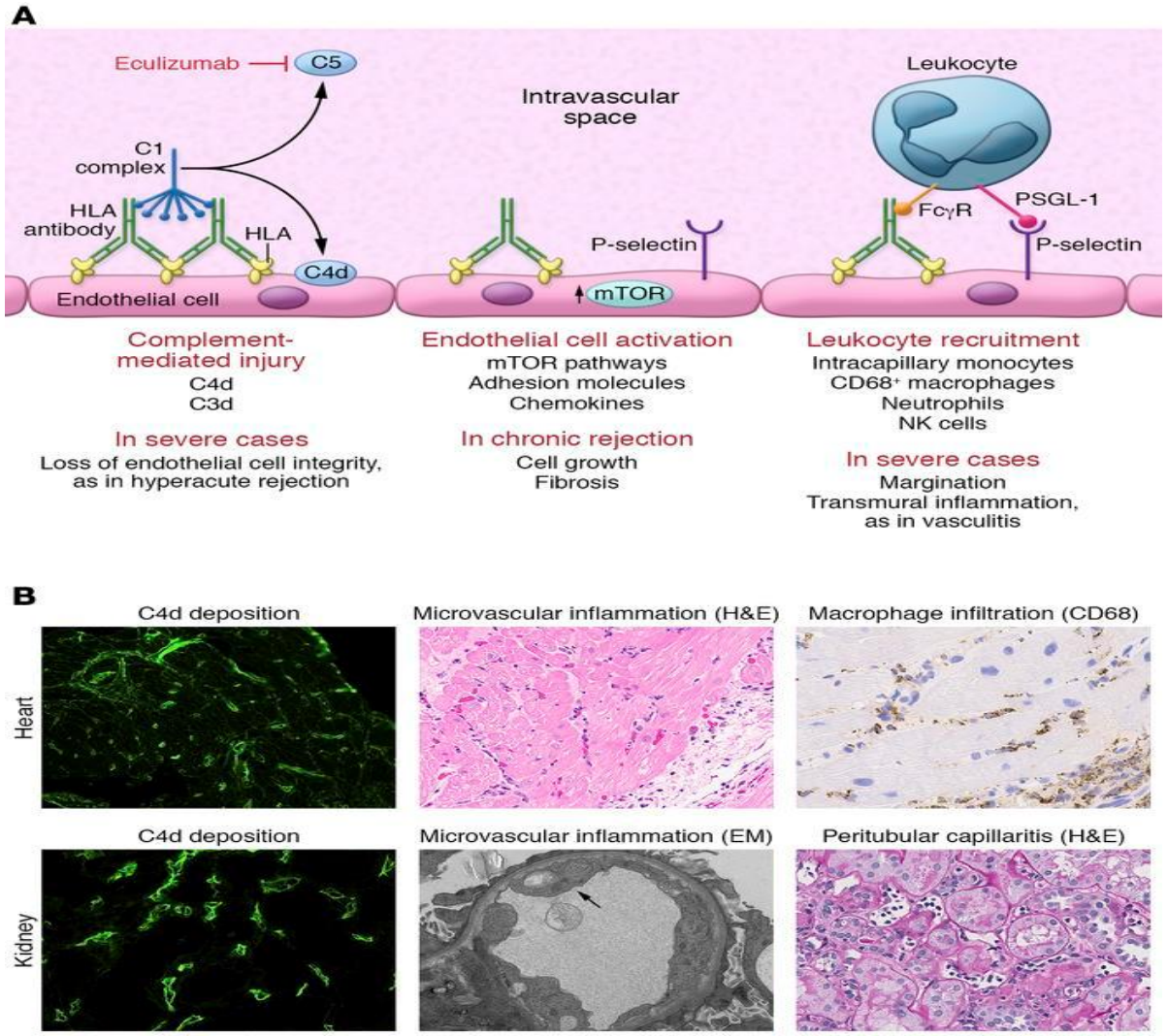
Features of transplant vasculopathy across solid organs and composite tissue allografts

Table 2. The features of transplant vasculopathy across solid organs and composite tissue allografts

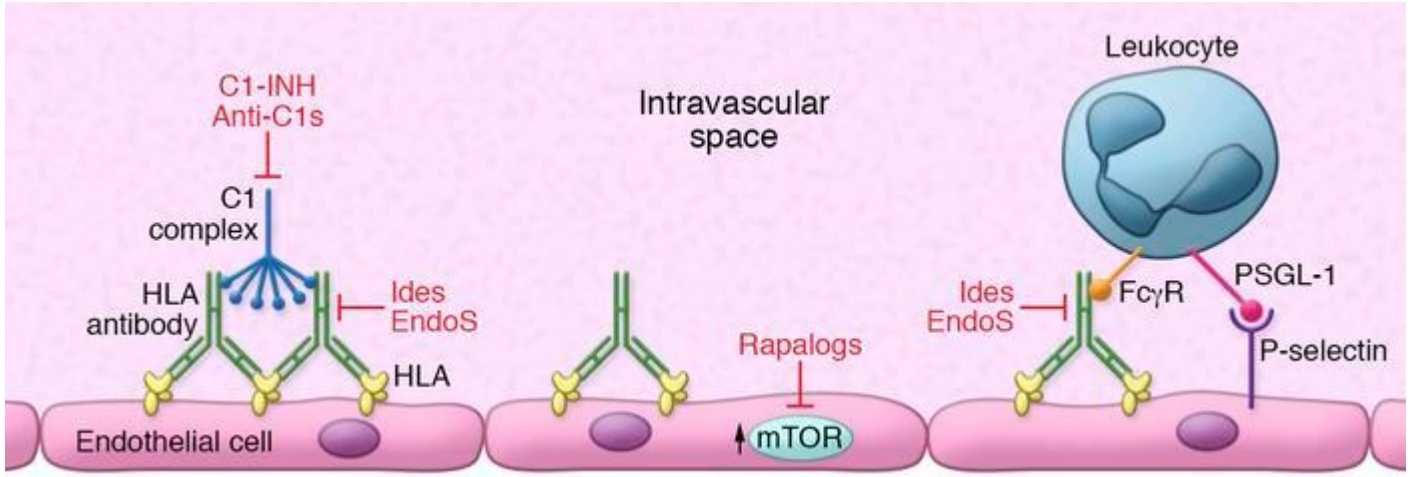
				Features of transplant vasculopathy			
Organ/ Tissue	Primary reference	See also	Organ-specific name	Vascular lesions	Fibrosis	Inflammatory component	Notes
Heart	29, 39	25, 40	Cardiac allograft vasculopathy or arteriosclerosis	Arteriosclerosis with concentric and diffuse proliferative lesions; epicardial and myocardial arteries; loss of capillaries/microvascular density; apparent with light microscopy/H&E	May have medial atrophy	May or may not be present with arteritis, endothelialitis, or transmural inflammation; may have concurrent acute microcirculation inflammation	Usually missed by endomyocardial biopsy; distinct from atherosclerotic plaques
Kidney	30	152, 173	Transplant glomerulopathy in glomerular capillaries; transplant arteriopathy in arteries, arterioles and other vessels	Glomerular hypertrophy; may also be a component of chronic arteriolar change (intimal fibrosis, transplant arteriopathy), luminal narrowing of arteries	Duplication of glomerular BM, multilamination of the peritubular capillary BM; neomedial formation and fibrosis in arteries	Often intracapillary mononuclear cells are present; may have concurrent acute glomerulitis	Visualized by light microscopy (severe) and ultrastructural (EM) for BM lamination
Pancreas	32	32	Arteriopathy; graft sclerosis	Luminal narrowing	Arterial intimal fibrosis	Accompanied by mononuclear cell infiltration	Larger vessels often missed on biopsy; accompanied by acinar loss
Lung	33	96	Chronic vascular rejection	Fibrointimal thickening of pulmonary arteries and veins	Intimal fibrosis of larger pulmonary vessels, may have medial atrophy	Mononuclear cell infiltration	Linked with but distinct from obliterative bronchiolitis, which affects the airways; often missed by transbronchial biopsy
Liver	31	28, 100, 118	Chronic rejection	Obliterative arteriopathy	Noninflammatory fibrosis	Mononuclear periportal and/ or perivenular inflammation; accumulation of foam cell macrophages in the intima	Accompanied by bile duct loss
Intestine	Not well defined (193)	197	Obliterative arteriopathy	Arteriopathy affecting the mesenteric and other submucosal arteries, concentric intimal thickening; intimal hyperplasia and luminal narrowing	Fibrosis of submucosa		Often missed by surveillance biopsy
Composite tissue	34	166	Chronic vasculopathy	Possibly vascular narrowing, myointimal proliferation; seen in major vessels (e.g., donor radial and ulnar arteries in hand)	Duplication of elastic lamina		Often missed by punch biopsy

Note that chronic AMR is a distinct diagnosis that is often concurrent with transplant vasculopathy. BM, basement membrane; EM, electron microscopy.

The known mechanisms of HLA antibody–mediated allograft injury and their therapeutic targets



Emerging therapies to inhibit HLA antibody–induced allograft injury



Current and emerging therapies to prevent HLA antibody production.