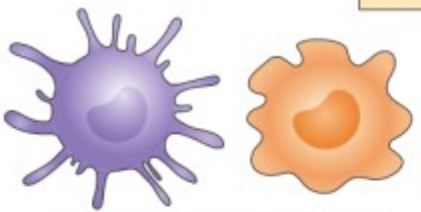
Antijen sunumu ve doku uyumluluk antijenleri

Professional APCs



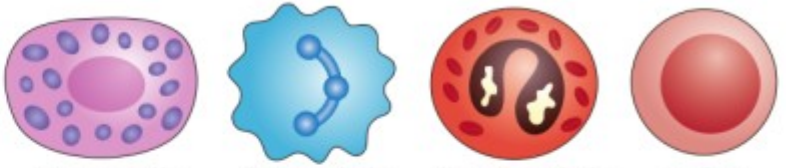
DCs and macrophages

B cells

Key features
- Phagocytic
- Express receptors for apoptotic cells, DAMPs and PAMPs
- Localize to tissues
- Localize to T cell zone of lymph nodes following activation (DCs)
- Constitutively express high levels of MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

Key features
- Internalize antigens via BCRs
- Constitutively express MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

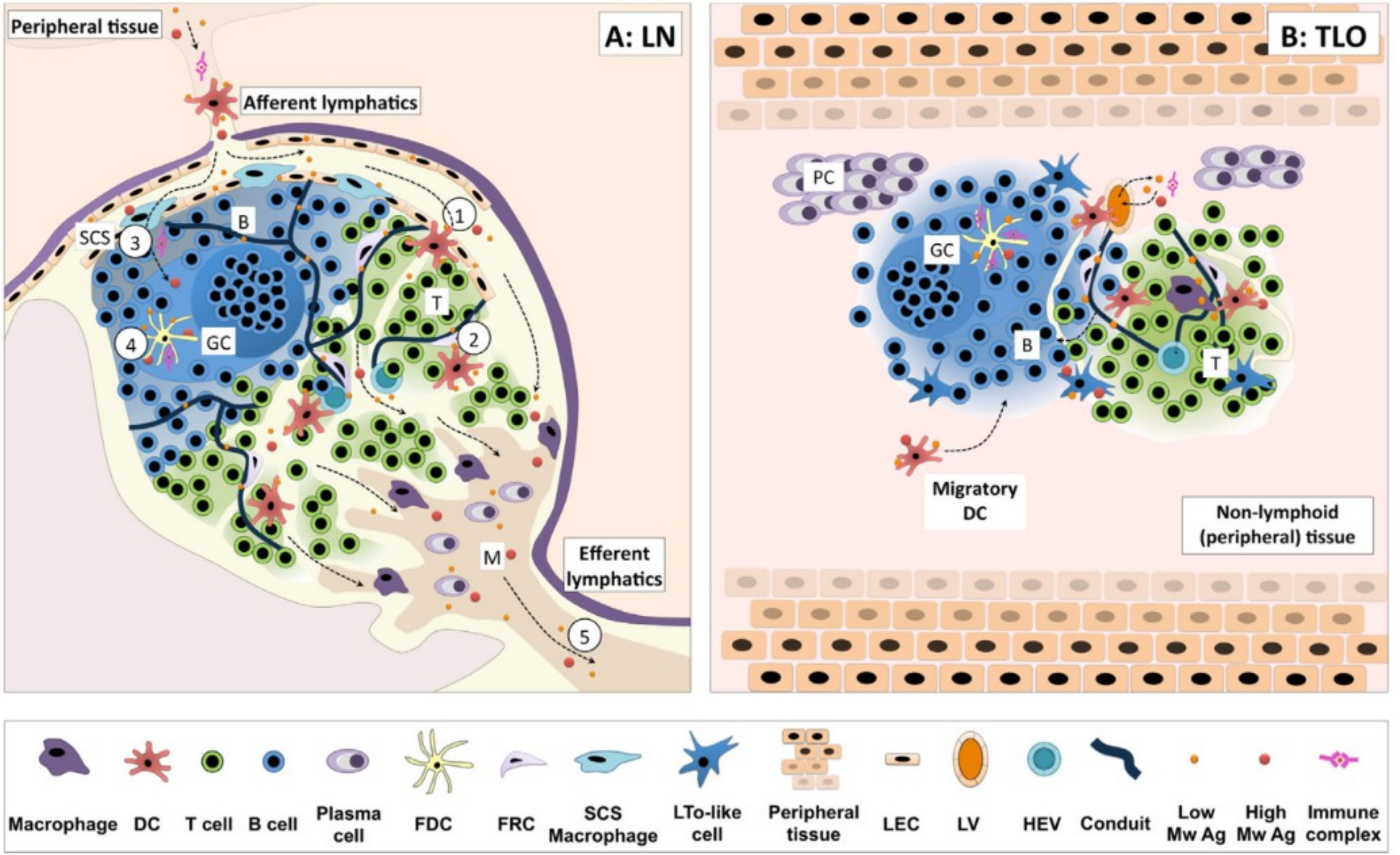
Atypical APCs



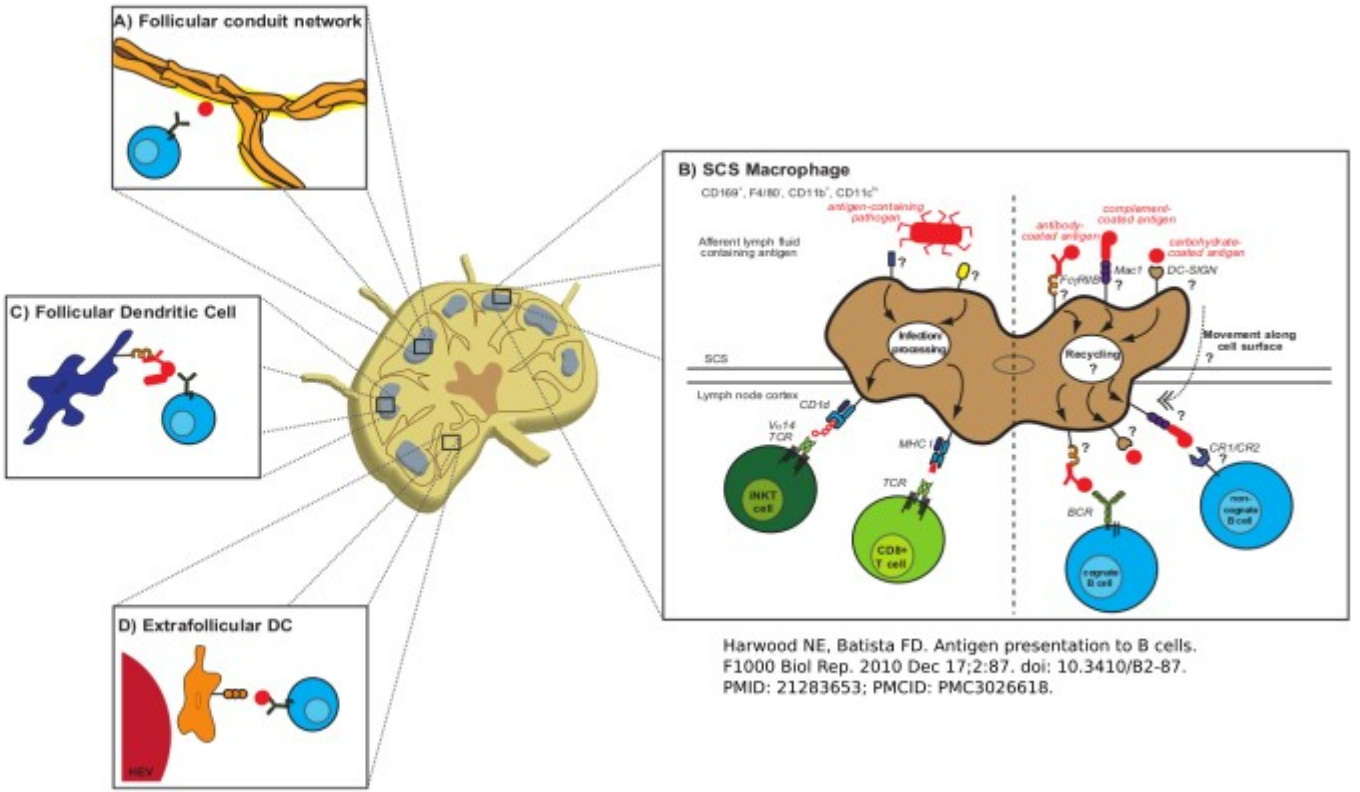
Mast cells Basophils Eosinophils ILC3s

Key features
- Inducible expression of MHC class II molecules
- Antigen-presenting functions limited to specific immune environments (especially type 2 immune settings)
- Lack of compelling evidence that they can activate naive $CD4^+$ T cells in an antigen-specific manner

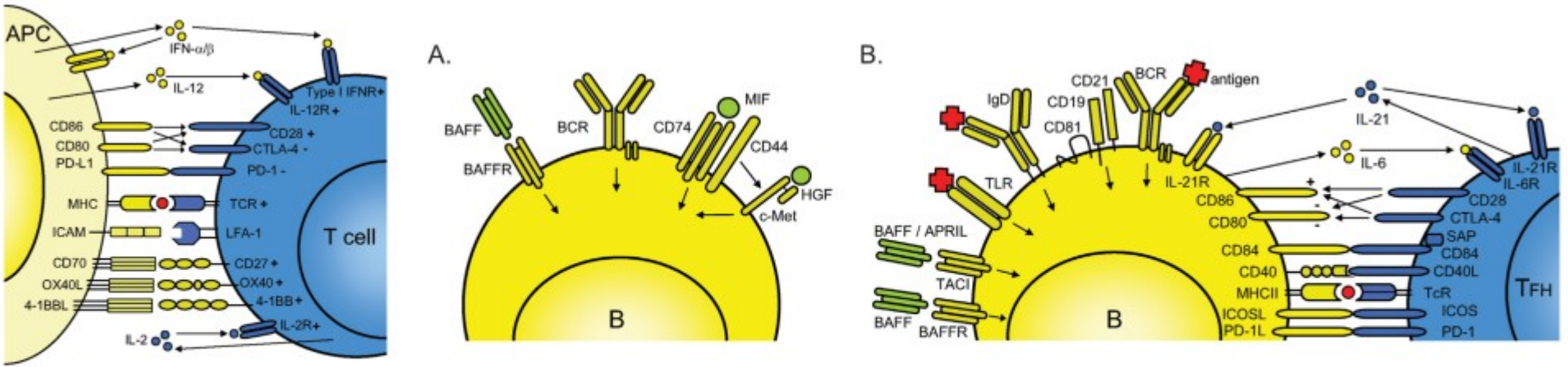
Kambayashi T, Laufer TM. Atypical MHC class II-expressing antigen-presenting cells: can anything replace a dendritic cell? Nat Rev Immunol. 2014 Nov;14(11):719-30. doi: 10.1038/nri3754. Epub 2014 Oct 17. PMID: 25324123.


Peripheral tissue
A: LN
Afferent lymphatics
SCS
B
T
GC
M
Efferent lymphatics
1
2
3
4
5
B: TLO
PC
GC
B
T
Migratory DC
Non-lymphoid (peripheral) tissue
Macrophage
DC
T cell
B cell
Plasma cell
FDC
FRC
SCS Macrophage
LTo-like cell
Peripheral tissue
LEC
LV
HEV
Conduit
Low Mw Ag
High Mw Ag
Immune complex

Hughes CE, Benson RA, Bedaj M, Maffia P. Antigen-Presenting Cells and Antigen Presentation in Tertiary Lymphoid Organs. Front Immunol. 2016 Nov 7;7:481. doi: 10.3389/fimmu.2016.00481. PMID: 27872626; PMCID: PMC5097899.



Harwood NE, Batista FD. Antigen presentation to B cells. F1000 Biol Rep. 2010 Dec 17;2:87. doi: 10.3410/B2-87. PMID: 21283653; PMCID: PMC3026618.



den Haan JM, Arens R, van Zelm MC. The activation of the adaptive immune system: cross-talk between antigen-presenting cells, T cells and B cells. Immunol Lett. 2014 Dec;162(2 Pt B):103-12. doi: 10.1016/j.imlet.2014.10.011. Epub 2014 Oct 16. PMID: 25455596.

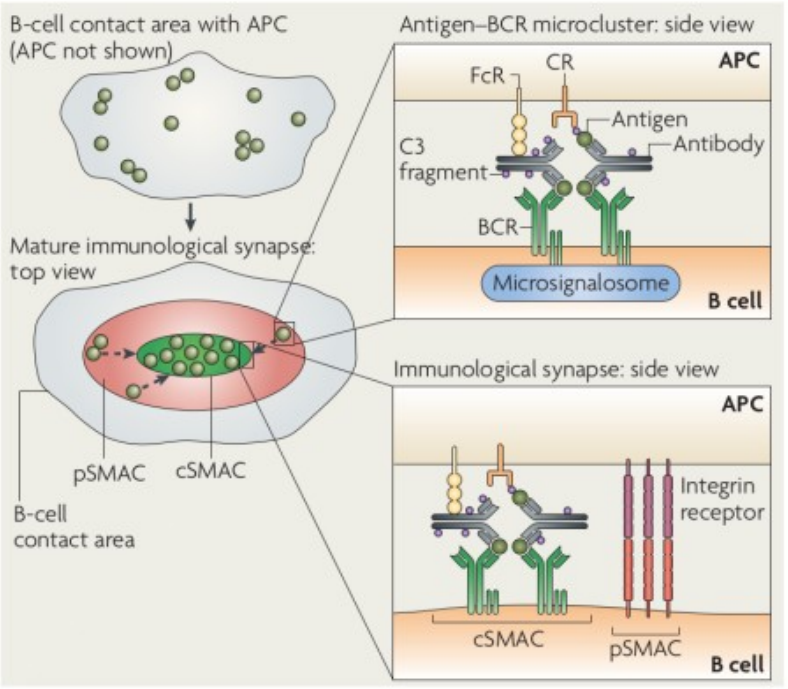
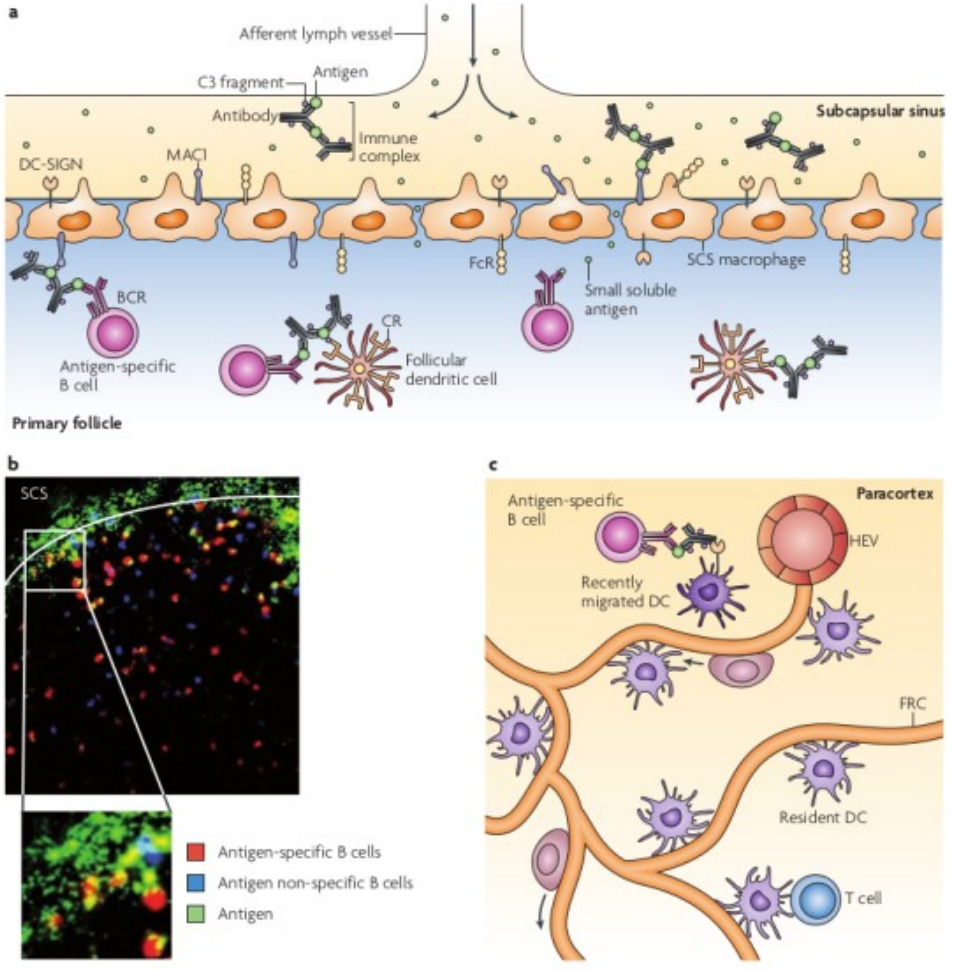


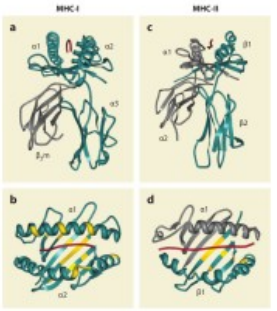
Table 1 | **Cell-surface molecules that are implicated in presenting antigen to B cells**

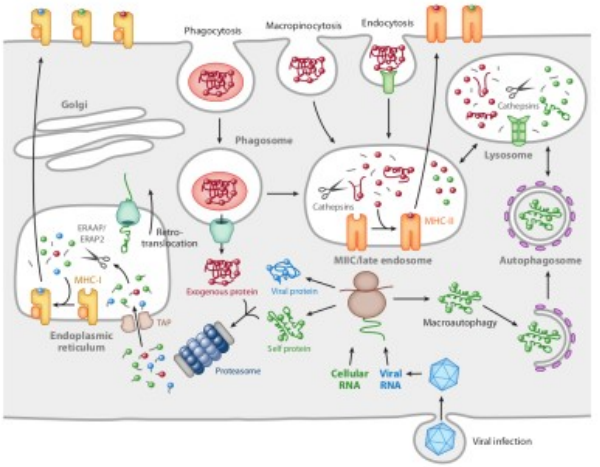
Presenting cell	Receptor	Antigen presented	Presentation strategy
Macrophage	MAC1	Complement-coated antigen	Remains on the cell surface
	FcγRIIB	IgG-coated antigen	Internalized in neutral endosomes and recycled?
	DC-SIGN	Carbohydrate-containing antigen	Internalized in neutral endosomes and recycled?
DC	FcγRIIB	IgG-coated antigen	Internalized in neutral endosomes and recycled?
	DC-SIGN	Carbohydrate-containing antigen	Internalized in neutral endosomes and recycled?
FDC	CR1 and CR2	Complement-coated antigen	Remains on the cell surface
	FcγRIIB	IgG-coated antigen	Internalized in neutral endosomes and recycled?
Marginal-zone B cell	CR1 and CR2	Complement-coated antigen	Remains on the cell surface
Follicular B cell	CR1 and CR2	Complement-coated antigen	Remains on the cell surface
	FcγRIIB	IgG-coated antigen	Internalized in neutral endosomes and recycled?

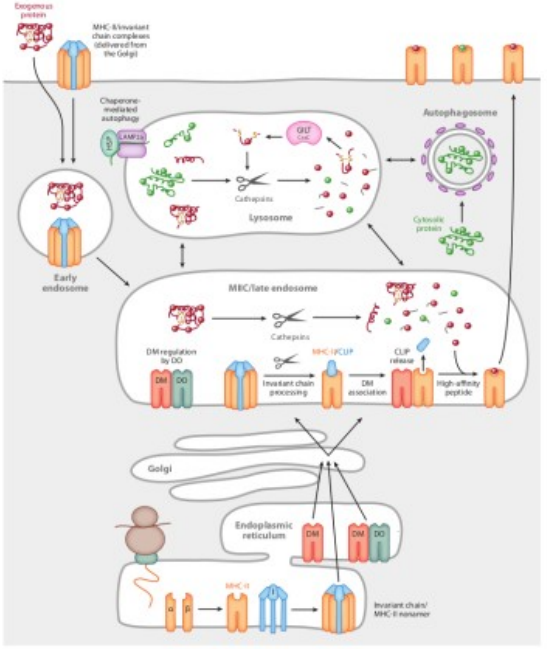


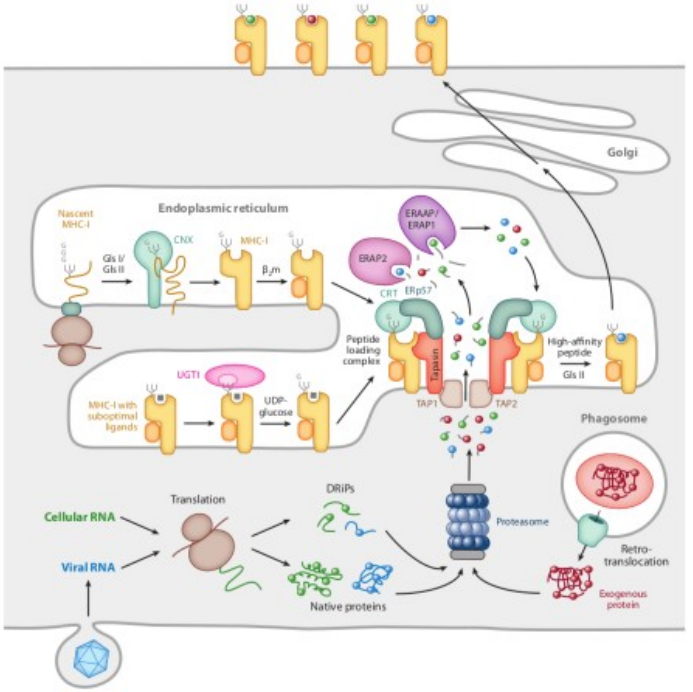
Batista FD, Harwood NE. The who, how and where of antigen presentation to B cells. Nat Rev Immunol. 2009 Jan;9(1):15-27. doi: 10.1038/nri2454. PMID: 19079135.

Blum JS, Wearsch PA, Cresswell P. Pathways of antigen processing. Annu Rev Immunol. 2013;31:443-73. doi: 10.1146/annurev-immunol-032712-095910. Epub 2013 Jan 3. PMID: 23298205; PMCID: PMC4026165.



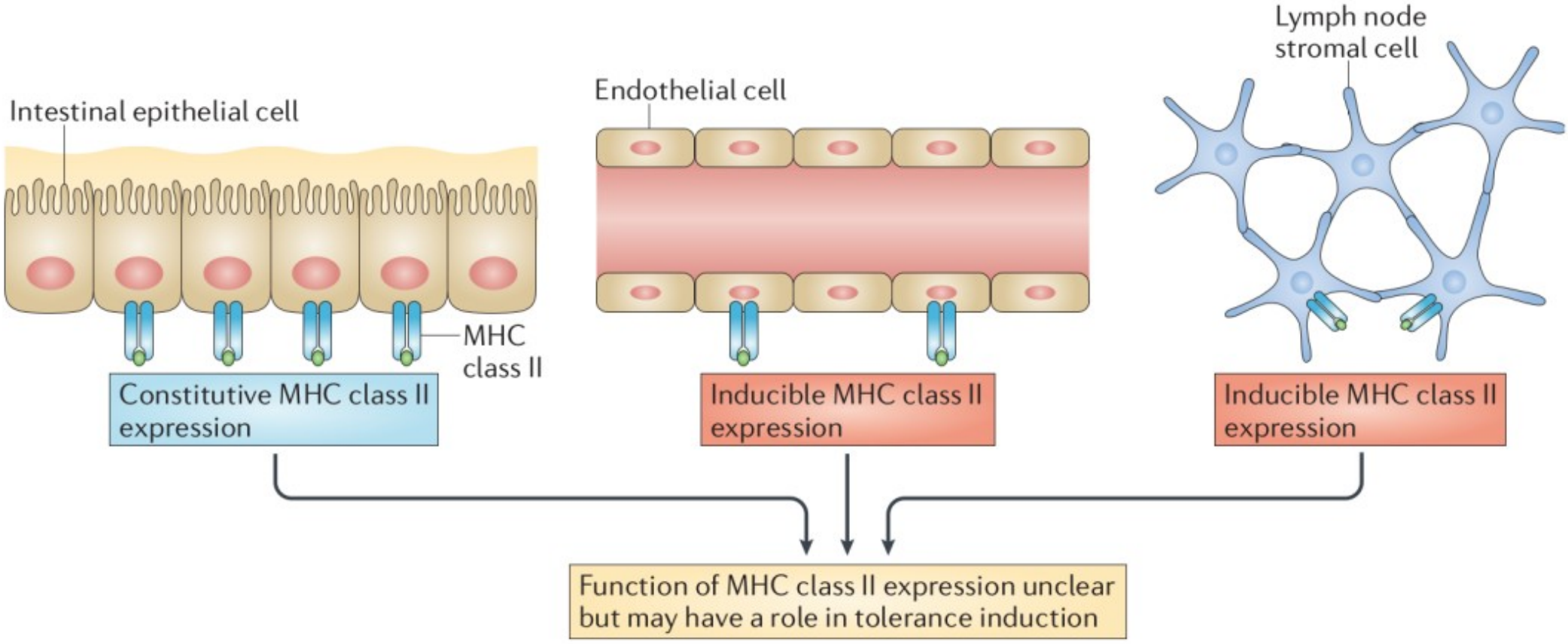




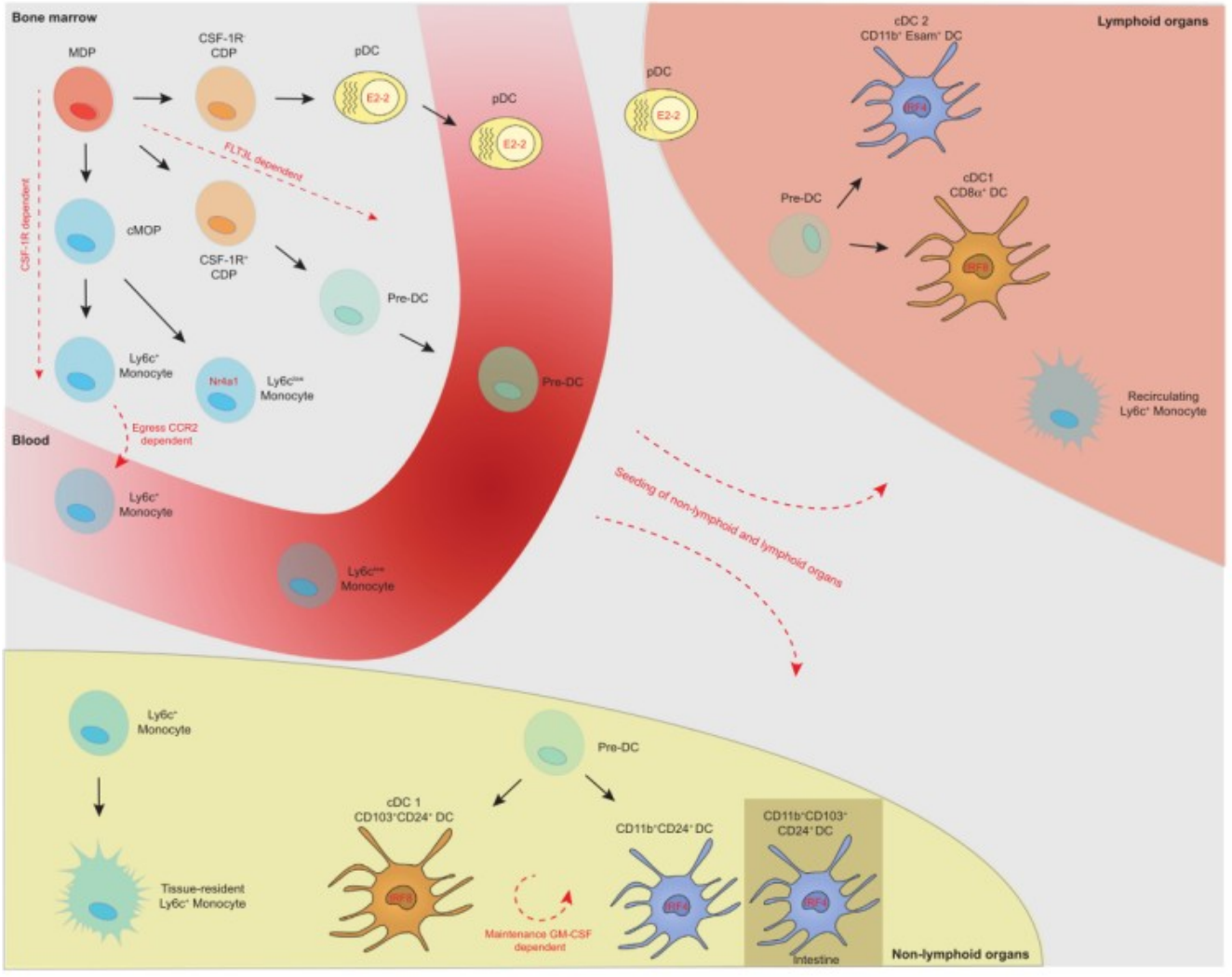


Atypical APC	Features of atypical APC					
	Ability to promote T cell activation		Expression of co-stimulatory molecules	Lymph node migration by APC	Factors that induce expression of MHC class II on APC	Expression of other MHC class II-related genes
	Naive T cells	Activated T cells				
Mast cells	+/–	+	+/– (CD80 and CD86)	+	TLR agonists, IFNγ, GM-CSF, IL-4 and Notch	Ii and HLA-DM
Basophils	+/–	+/–	+ (mouse) – (human)	+	FcεRI, IL-3 and papain	Ii and HLA-DM
Eosinophils	+	+	CD80 and CD86	+	IL-3, IFNγ and GM-CSF	Unknown
Neutrophils	+/–	+/–	CD80 and CD86	+	Co-culture with T cells, GM-CSF and IFNγ	Unknown
ILC2s	+	Unknown	Unknown	Unknown	Unknown	Unknown
ILC3s	–	Tolerance induction	–	+	Unknown	Ii and HLA-DM
$CD4^+$ T cells	–	Tolerance induction	–	+	TCR stimulation	Unknown
LNSCs	Tolerance induction	Unknown	ICOSL (subset)	NA	TLR agonists and IFNγ	Ii and HLA-DM
Endothelial cells	–	+	CD137L, OX40L and ICOSL	–	IFNγ	Unknown
Epithelial cells	Tolerance induction	+	–	–	IFNγ and microbial stimuli	Ii and HLA-DM

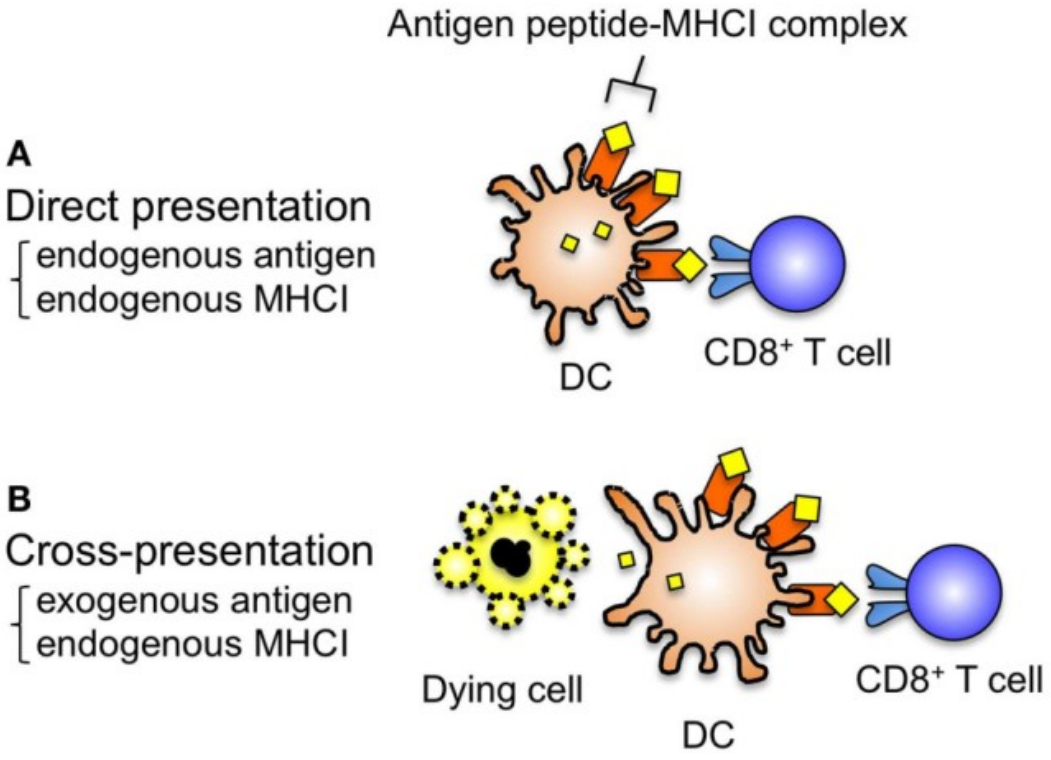
APC, antigen-presenting cell; CD137L, CD137 ligand (also known as TNFSF9); FcεRI, high-affinity Fc receptor for IgE; GM-CSF, granulocyte–macrophage colony-stimulatory factor; ICOSL, ICOS ligand; IFN, interferon; Ii, invariant chain; IL, interleukin; ILC, innate lymphoid cell; LNSC, lymph node stromal cell; NA, not applicable; OX40L, OX40 ligand (also known as TNFSF4); TCR, T cell receptor; TLR, Toll-like receptor.

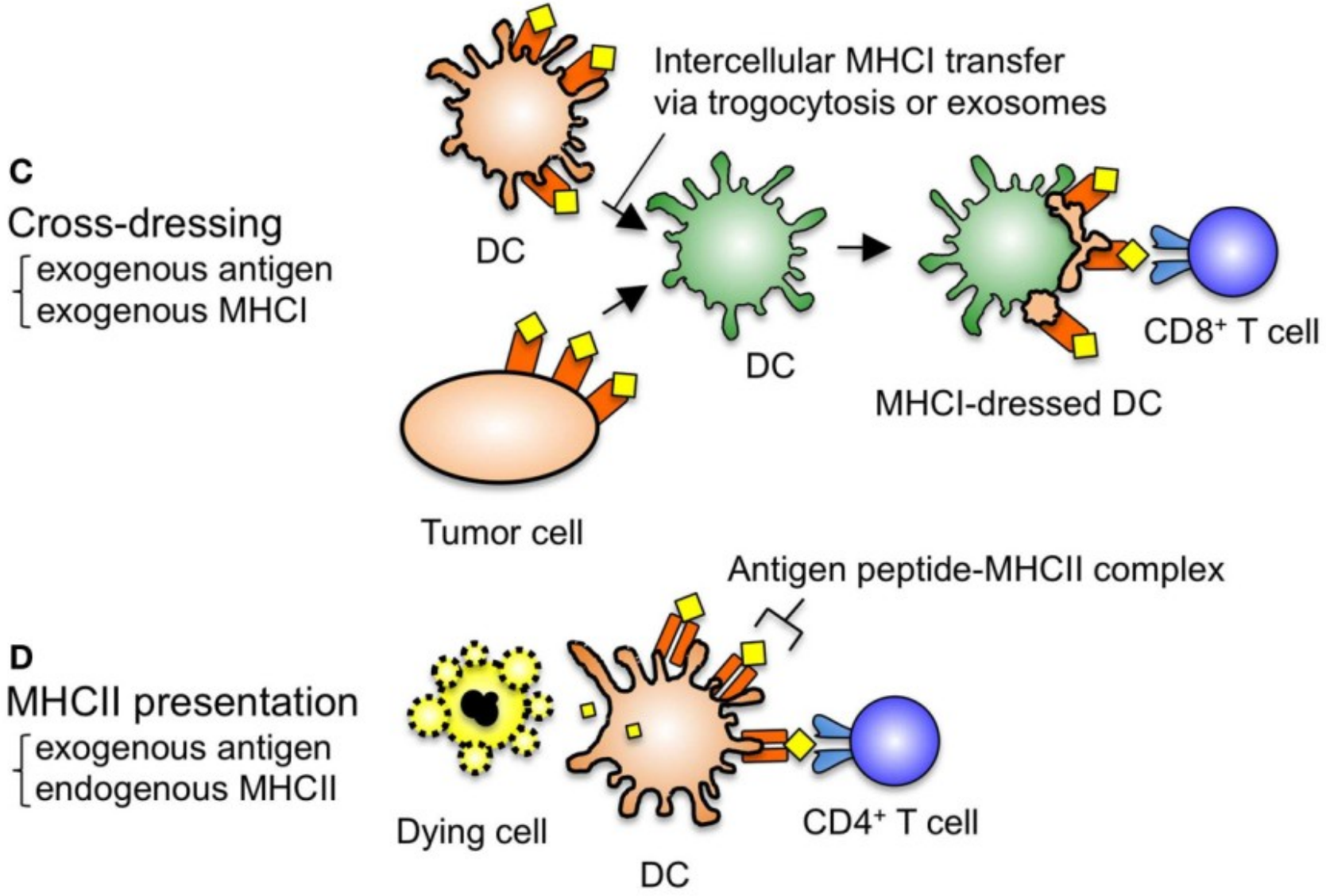

Intestinal epithelial cell
MHC class II
Constitutive MHC class II expression
Endothelial cell
Inducible MHC class II expression
Lymph node stromal cell
Inducible MHC class II expression
Function of MHC class II expression unclear but may have a role in tolerance induction

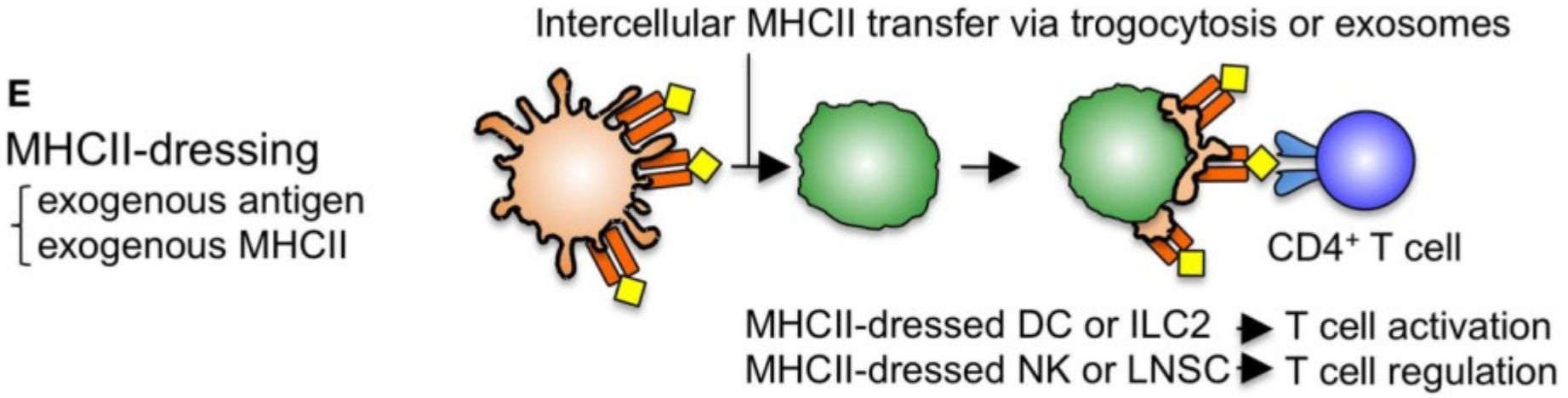
Schlitzer A, McGovern N, Ginhoux F. Dendritic cells and monocyte-derived cells: Two complementary and integrated functional systems. Semin Cell Dev Biol. 2015 May;41:9-22. doi: 10.1016/j.semcdb.2015.03.011. Epub 2015 May 6. PMID: 25957517.



DCs & nonAPCs acquire MHCI/II: trogocytosis




C
Cross-dressing
exogenous antigen
exogenous MHCI
Intercellular MHCI transfer
via trogocytosis or exosomes
DC
DC
CD8+ T cell
MHCI-dressed DC
Tumor cell
D
MHCII presentation
exogenous antigen
endogenous MHCII
Antigen peptide-MHCII complex
Dying cell
CD4+ T cell
DC

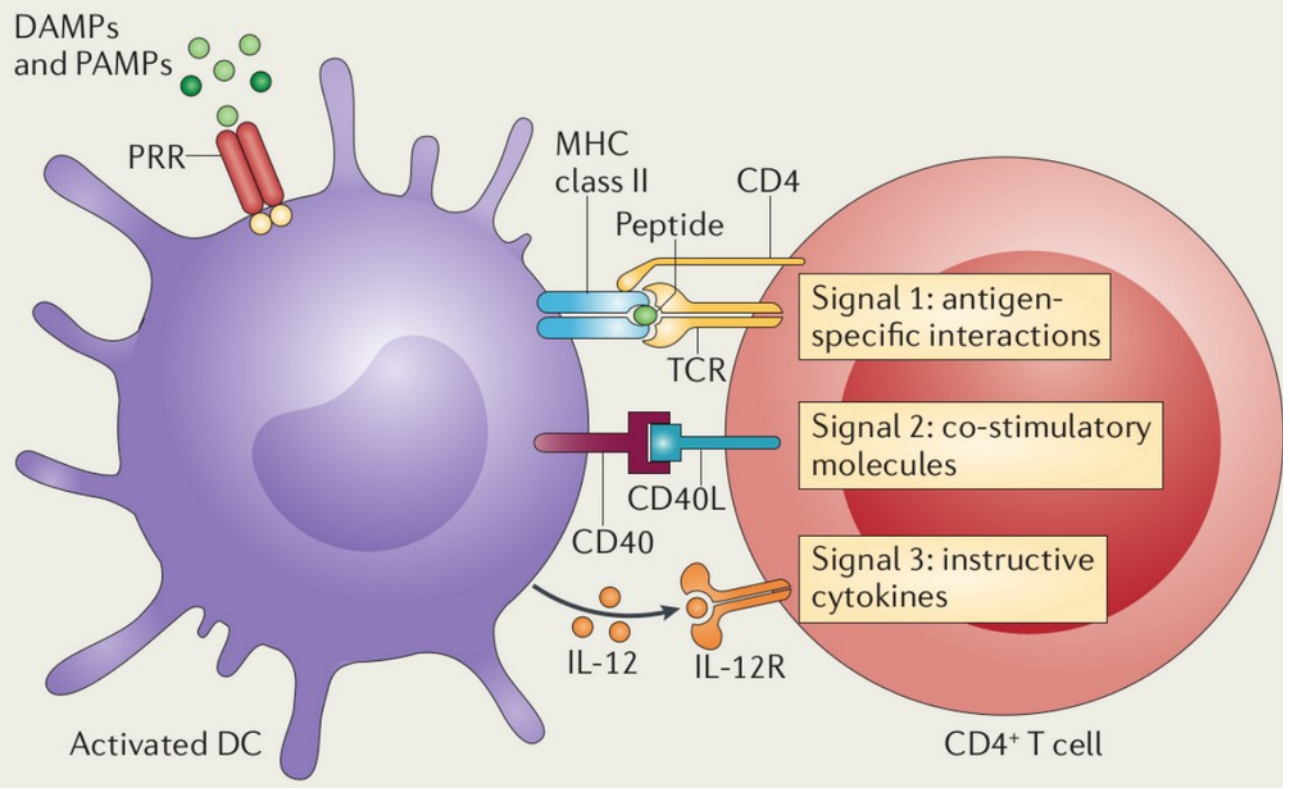


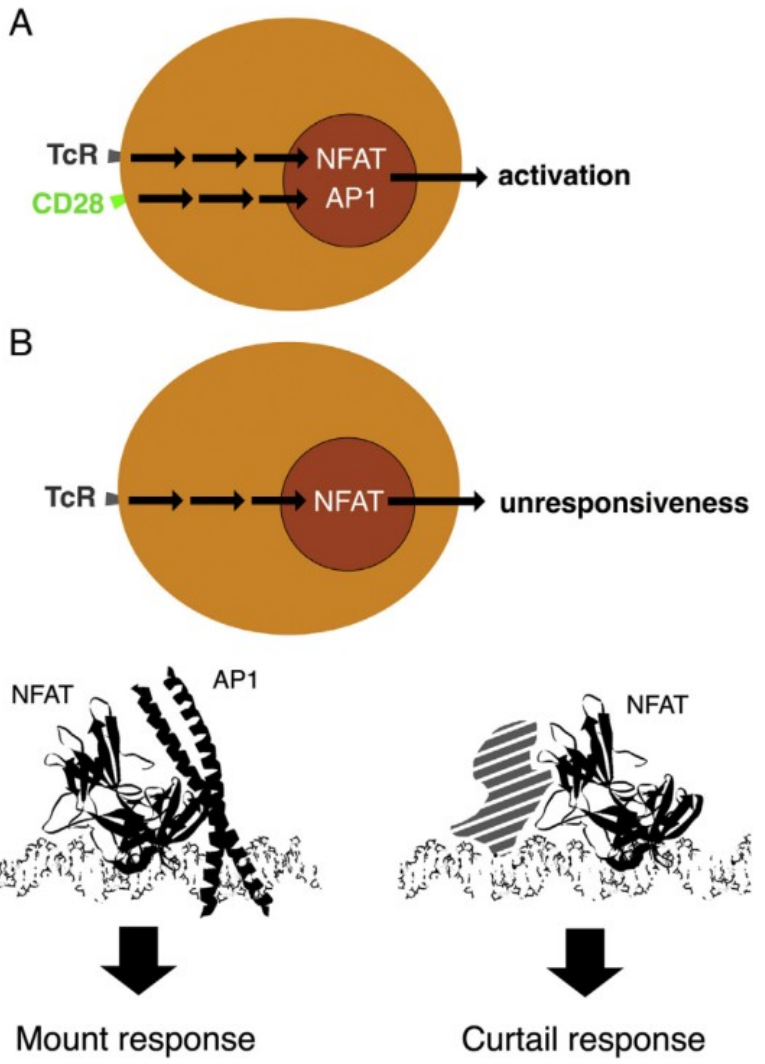
Nakayama M. Antigen Presentation by MHC-Dressed Cells.
Front Immunol. 2015 Jan 5;5:672. doi: 10.3389/fimmu.2014.00672.
PMID: 25601867; PMCID: PMC4283639.

Donor cell	Recipient cell	Mechanism	Function (Ref)
INTERCELLULAR MHCI TRANSFER			
APCs (DCs)	$CD8^+$ T cells	Trogocytosis (TCR-mediated)	Target for neighboring CTLs: fratricide (2, 4) TCR downregulation (7) Unknown (3)
Live tumor cells	$CD8^+$ T cells	Trogocytosis (TCR-mediated)	Target for neighboring CTLs: fratricide (19) Enhancement of CTL activity? (20) Suppression of CTL activity? (21) Stripping MHCI off target tumor cells (8)
APCs	$CD4^-$ $CD8^-$ Tregs	Trogocytosis (TCR-mediated)	Antigen presentation for $CD8^+$ T cell suppression (22)
DCs	$CD4^+$ T cells	Trogocytosis (TCR-mediated bystander)	Antigen presentation for $CD8^+$ T cell activation (23)
Live tumor cells	NK cells	Trogocytosis (KIR-mediated)	Suppression of neighboring NK cells (24) Unknown (25, 26)
Splenocytes	NK cells	Unknown	Enhancement of killer activity (27)
DCs	DCs	Trogocytosis	Antigen presentation for $CD8^+$ T cell activation: cross-dressing (28–30)
DCs, ECs	DCs	Exosomes	Antigen presentation for $CD8^+$ T cell activation: cross-dressing (31, 32)
Live tumor cells	DCs	Exosomes	Antigen presentation for $CD8^+$ T cell activation (33)
Live tumor cells	DCs	Trogocytosis?	Target for neighboring CTLs (34)
Dead tumor cells	DCs, pDCs	Trogocytosis	Antigen presentation for $CD8^+$ T cell activation (35–37)

INTERCELLULAR MHCII TRANSFER			
mTECs	Thymic DCs	Unknown	Antigen presentation for central tolerance (38–40)
APCs (DCs)	$CD4^+$ T cells	Trogocytosis (TCR-mediated)	Sustaining of TCR signaling (41, 42) Antigen presentation for $CD4^+$ T cell suppression (17, 18) Antigen presentation for $CD4^+$ T cell activation (43–45)
APCs (DCs)	$CD4^+$ T cells	Exosomes	Antigen presentation for $CD4^+$ T cell suppression (46, 47) Unknown (48)
APCs	$CD4^+$ Tregs	Trogocytosis (TCR-mediated)	Antigen presentation for $CD4^+$ T cell suppression (44)
DCs	$CD8^+$ T cells	Trogocytosis (TCR-mediated bystander)	Antigen presentation for $CD4^+$ T cell activation? (3, 49)
DCs	NK cells	Trogocytosis	Antigen presentation for $CD4^+$ T cell suppression (50)
DCs	ILC2s	Trogocytosis	Antigen presentation for $CD4^+$ T cell activation (51)
DCs	LNSCs	Trogocytosis and exosomes	Antigen presentation for $CD4^+$ T cell suppression (52)
DCs	DCs	Exosomes	Antigen presentation for $CD4^+$ T cell activation (31, 53, 54)
Dead tumor cells	DCs	Trogocytosis?	Antigen presentation for $CD4^+$ T cell activation (55)
APCs	DCs	Unknown	No antigen-presenting activity (56)

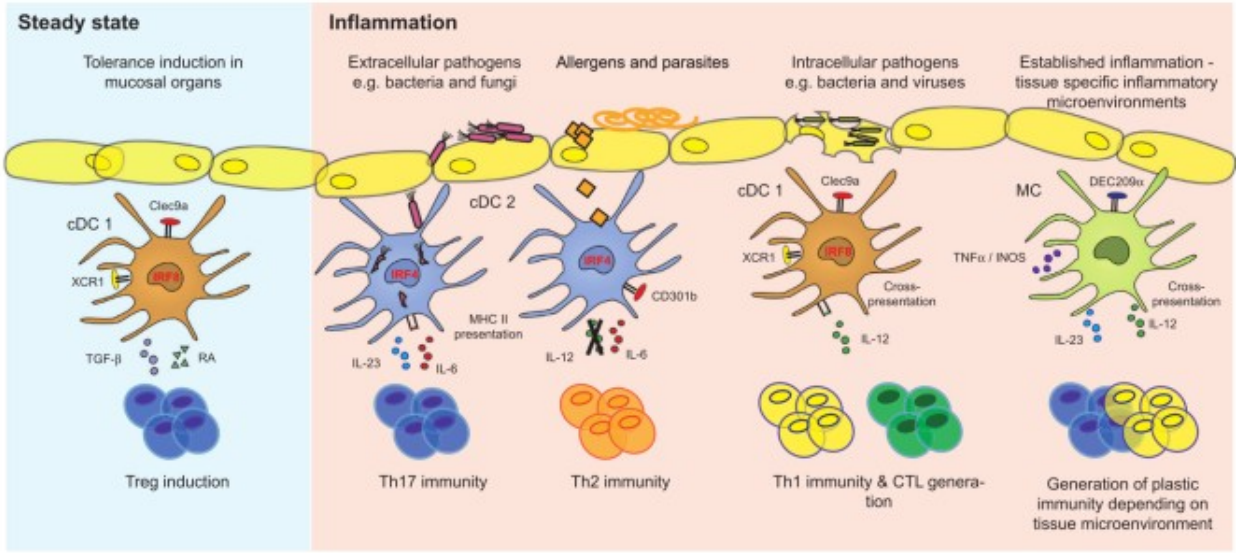
APCs, antigen-presenting cells; CTLs; cytotoxic T lymphocytes; DCs, dendritic cells; ECs, endothelial cells; ILC2s, group 2 innate lymphoid cells; KIR, killer cell immunoglobulin-like receptor; LNSCs, lymph node stromal cells; MHCI, MHC class I; MHCII, MHC class II; mTECs, medullary thymic epithelial cells; NK, natural killer; pDCs, plasmacytoid DCs; TCR, T cell receptor; Tregs, regulatory T cells.

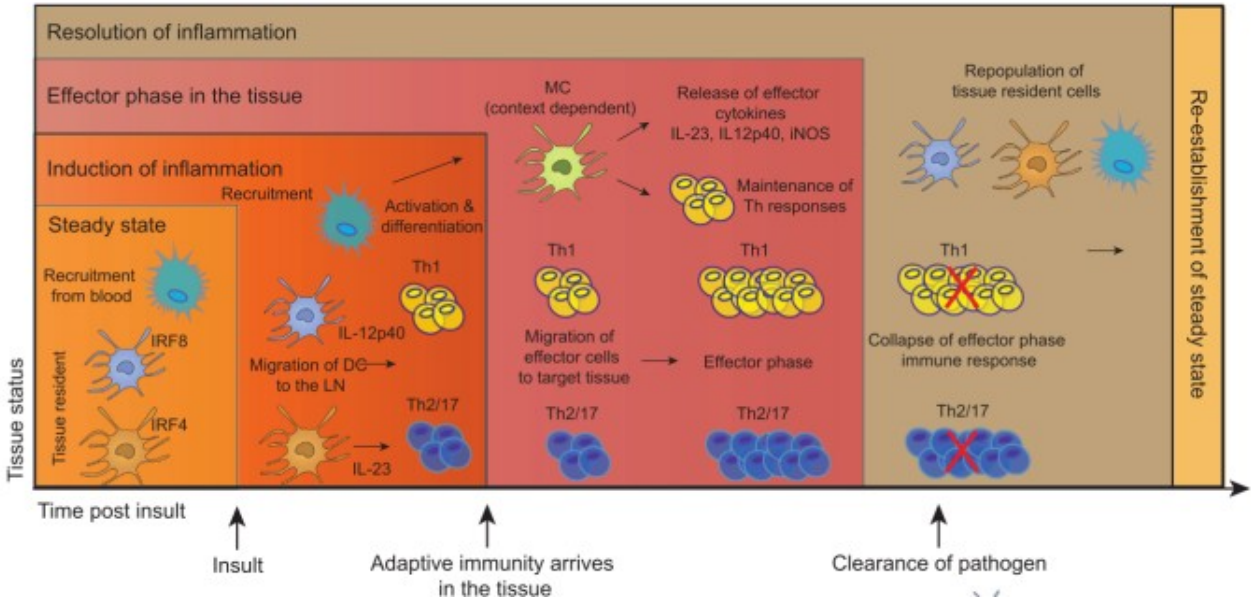




Hogan PG. Calcium-NFAT transcriptional signalling in T cell activation and T cell exhaustion. Cell Calcium. 2017 May;63:66-69. doi: 10.1016/j.ceca.2017.01.014. Epub 2017 Jan 28. PMID: 28153342; PMCID: PMC5739523.

cDC1			cDC2		Monocyte-derived macrophages		Inflammatory monocyte-derived cells	
Species	Mouse	Human	Mouse	Human	Mouse	Human	Mouse	Human
Phenotype	CD8α (LT) CD103 (NLT) Clec9a XCR1 CADM1	CD11c$^{lo/-}$ BTLA CD141 CD103 (gut) Clec9a XCR1 CADM1 CD26 CXCR3	CD11b CD24 CD103 (gut) CD301b	CD11c BTLA$^{+/lo}$ CD1c SIRPα CD1a$^{+/lo}$ CD11b$^{-/+}$ CD103 (gut)	CX3CR1 CD14 CD24^{lo} MerTK CD11c MHC-II CCR2	CD209 CD14 CD64 CD163 CD11c CD141 SSC-A^{lo} Af^{lo} CD16$^{+/-}$ CX3CR1 SIRPα	Ly6c CD11b CD209α CD11c CD206 CD64 FcεR1 MHC-II	CD14 CD1c CD1a CD206 CD11b SIRPα CD64 FcεR1 SLAN TF Zbtb46
PAMP	TLR3 TLR4 TLR11 TLR13	TLR3 TLR8	TLR5 TLR6 TLR7 TLR9 TLR13 RIG-1 Dectin 1 Dectin 2	TLR1 TLR2 TLR3 TLR4 TLR5 TLR6 TLR7 TLR8 Clec6a Clec7a	Not fully verified	TLR1 TLR2 TLR5 TLR8	Not fully verified	
Th polarization	Th1	Th1	Th17 Th2	Th17 Th2 Treg Th1	Not fully verified	Treg	Not fully verified	Th17


Steady state
Inflammation
Tolerance induction in mucosal organs
Extracellular pathogens e.g. bacteria and fungi
Allergens and parasites
Intracellular pathogens e.g. bacteria and viruses
Established inflammation - tissue specific inflammatory microenvironments
cDC 1
Clec9a
XCR1
IRF8
TGF-β
RA
cDC 2
IRF4
MHC II presentation
IL-23
IL-6
CD301b
IL-12
cDC 1
Clec9a
XCR1
IRF8
Cross-presentation
IL-12
MC
DEC209α
TNFα / iNOS
Cross-presentation
IL-12
IL-23
Treg induction
Th17 immunity
Th2 immunity
Th1 immunity & CTL generation
Generation of plastic immunity depending on tissue microenvironment


Resolution of inflammation
Effector phase in the tissue
Induction of inflammation
Steady state
Recruitment from blood
IRF8
IRF4
Tissue resident
Recruitment
Activation & differentiation
Th1
IL-12p40
Migration of DC to the LN
Th2/17
IL-23
MC (context dependent)
Release of effector cytokines IL-23, IL12p40, iNOS
Maintenance of Th responses
Th1
Th1
Migration of effector cells to target tissue
Effector phase
Th2/17
Th2/17
Repopulation of tissue resident cells
Th1
Collapse of effector phase immune response
Th2/17
Re-establishment of steady state
Tissue status
Time post insult
Insult
Adaptive immunity arrives in the tissue
Clearance of pathogen