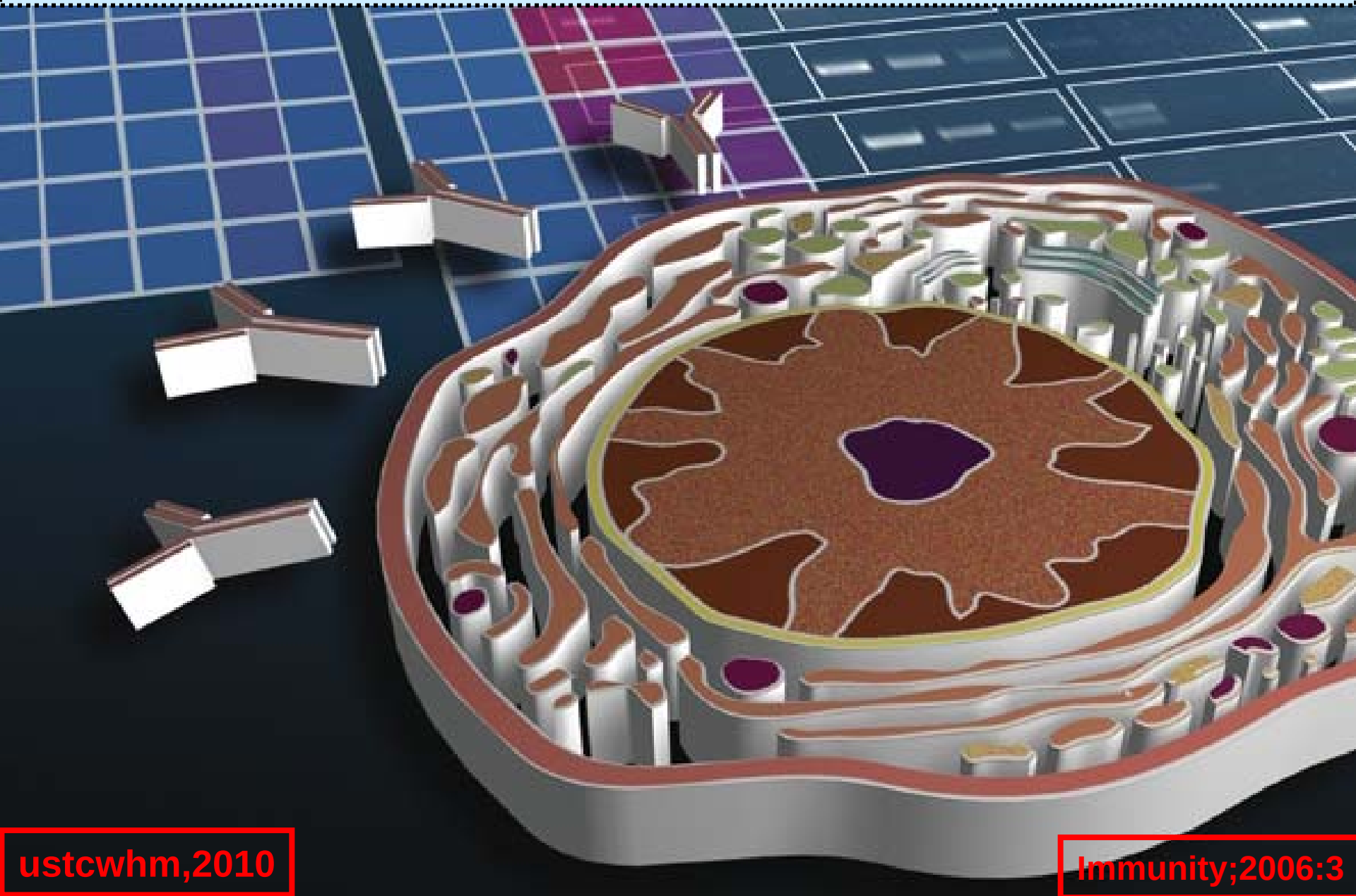
B lymphocyte



ustcwhm,2010

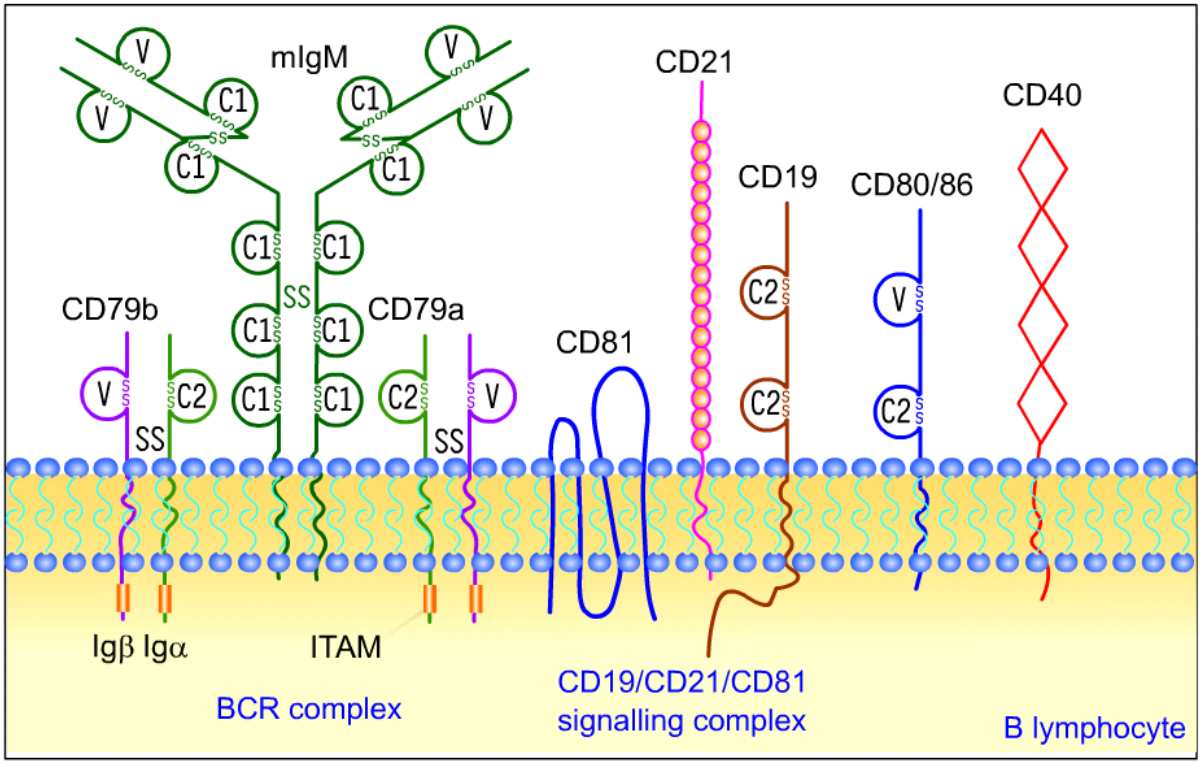
Immunity;2006:3

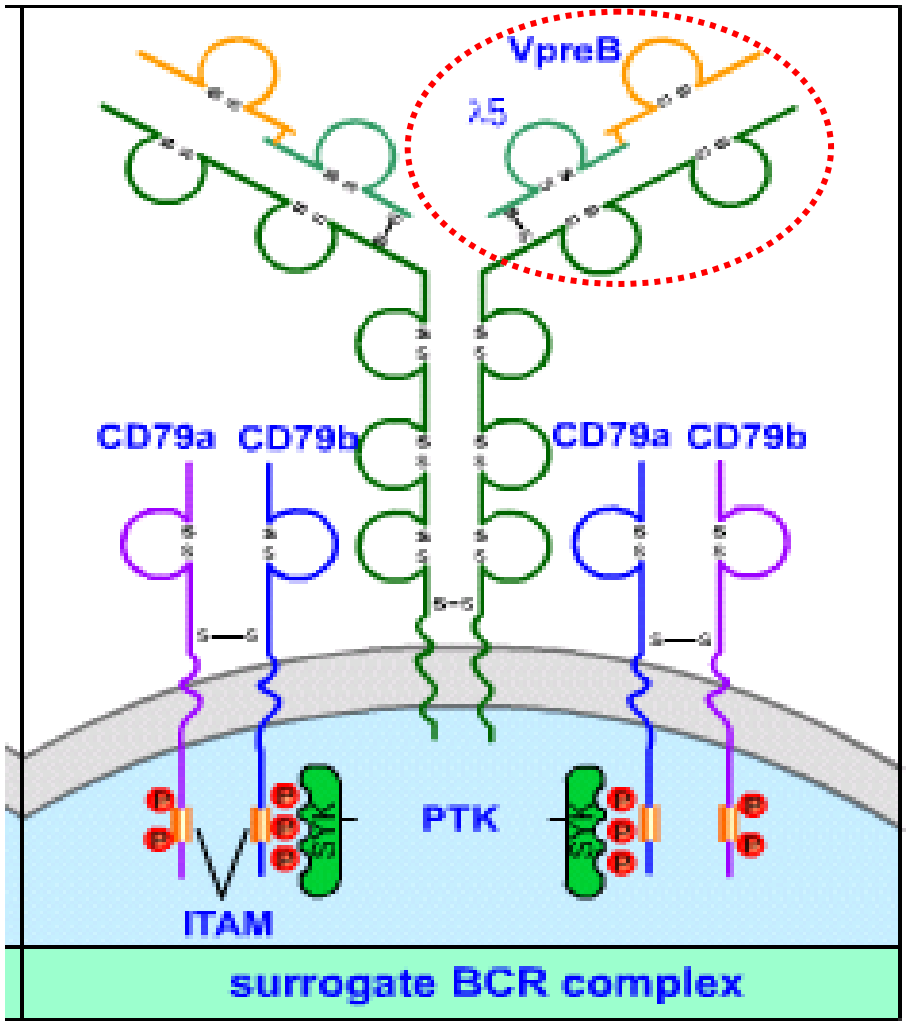
1. Surface Molecules

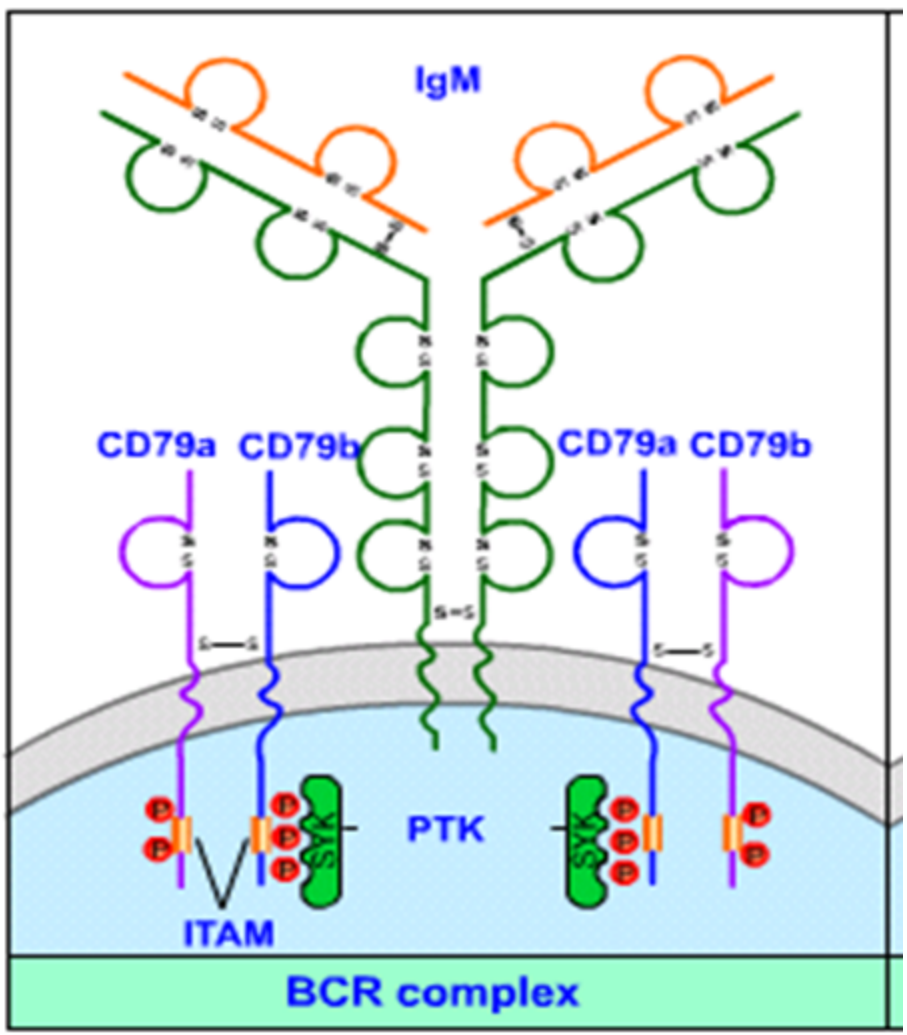
1.1 BCR complex: mIgM, mIgD / CD79a(Ig α),CD79b(Ig β)

1.2 CD19, CD21, CD81 / CD40, CD80, CD86

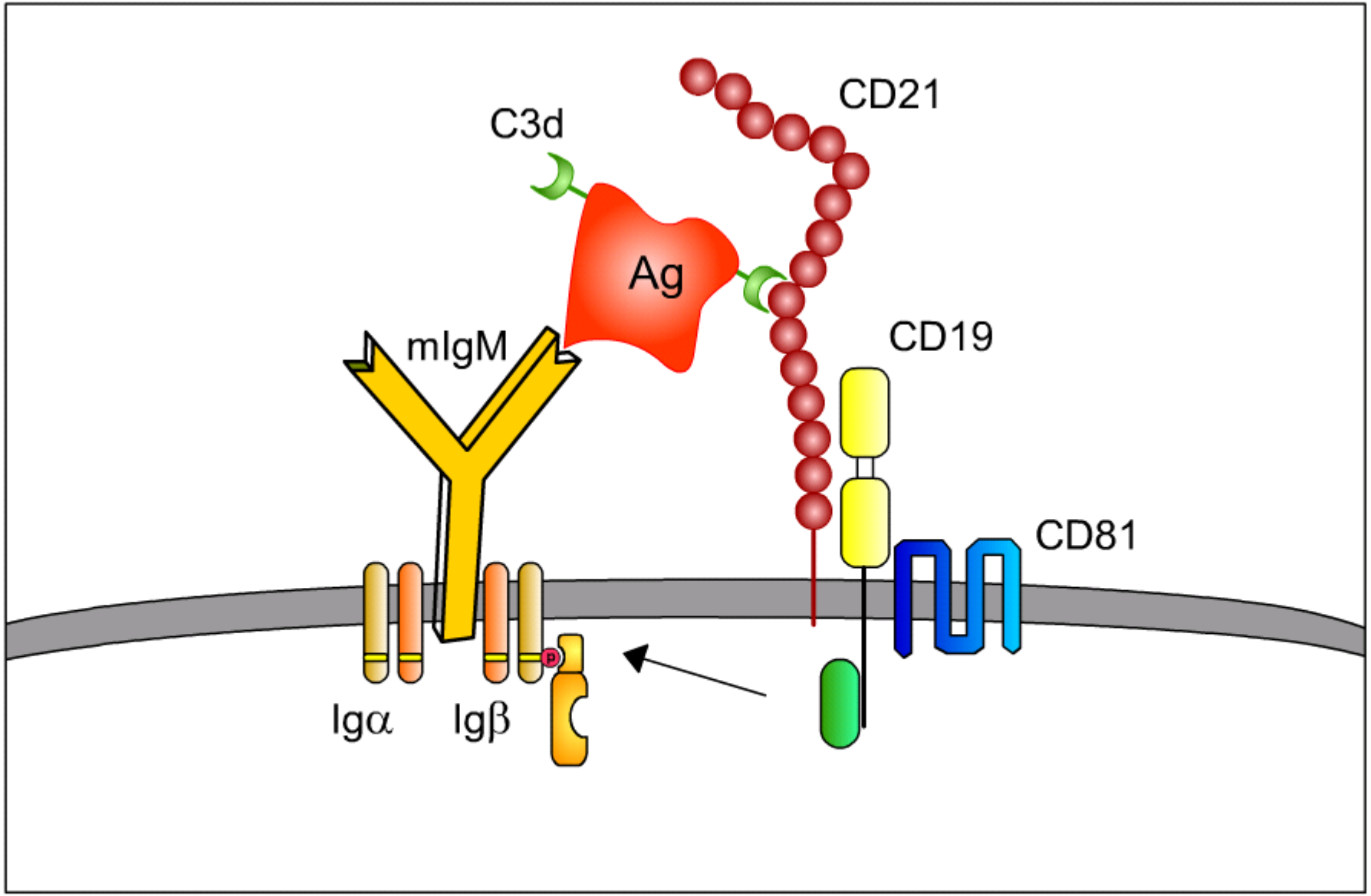
1.3 CR1(CD35, C3bR) / CR2(CD21,C3dR, EBV-R)







BCR complex and surrogate BCR complex



B cell sigalling complex

Immunology

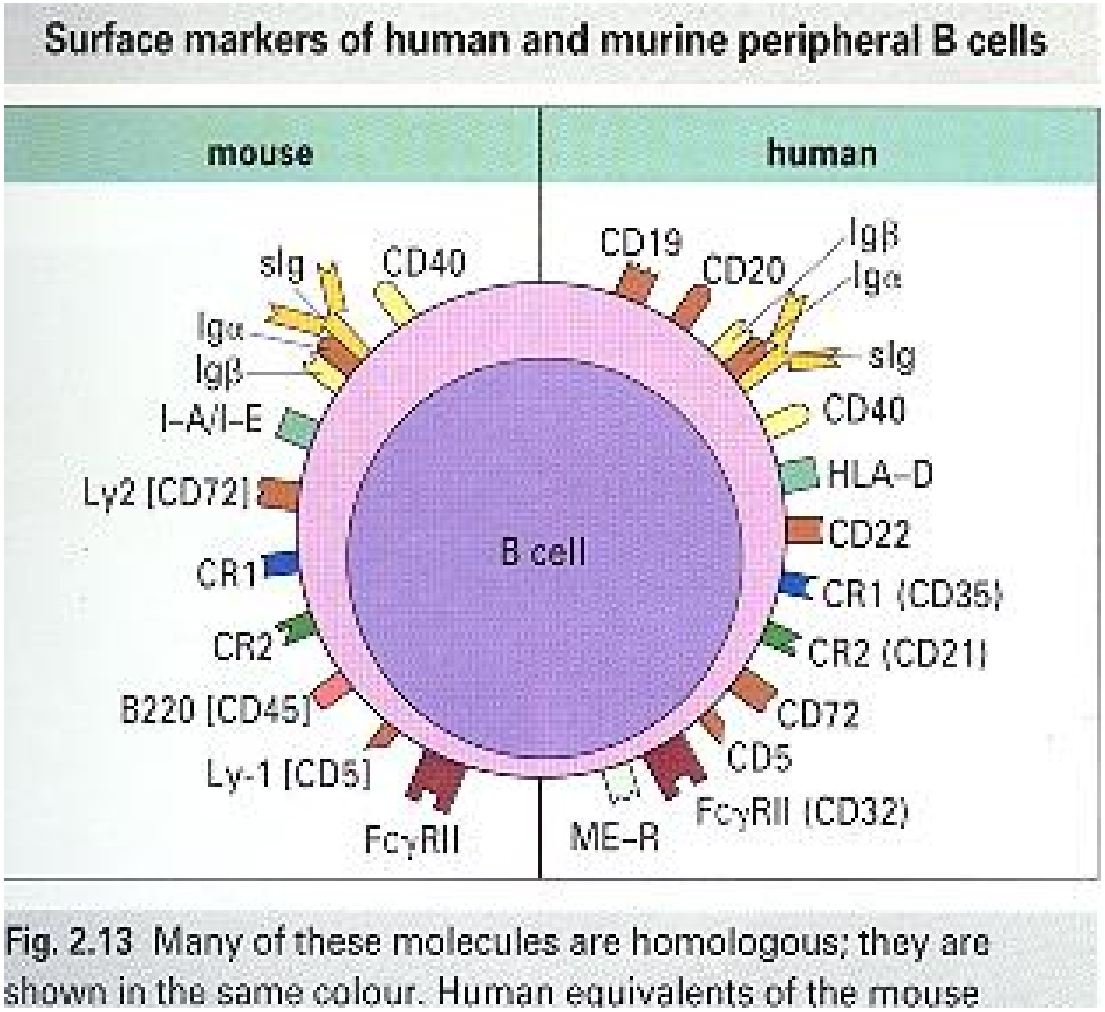
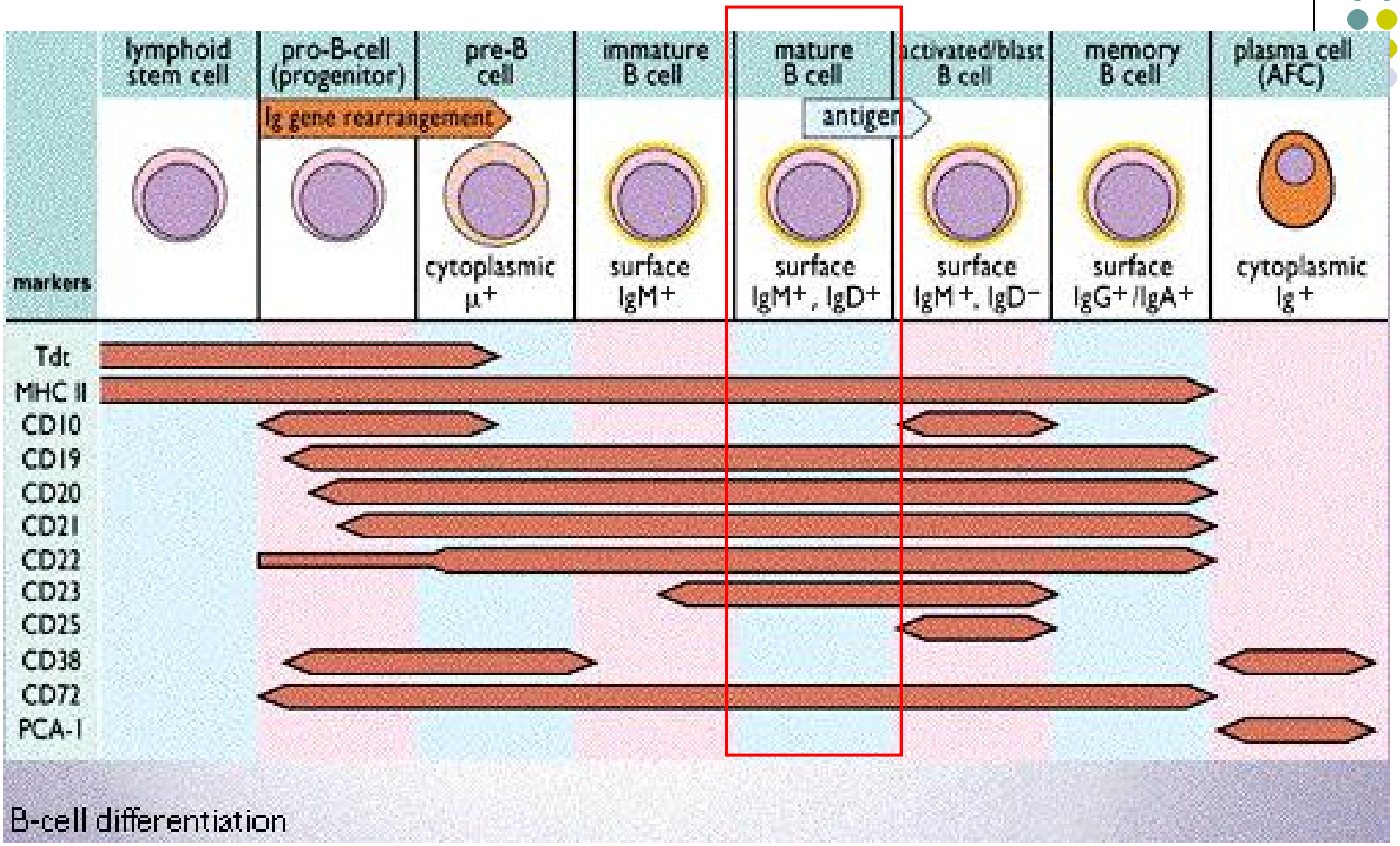


Fig. 2.13 Many of these molecules are homologous; they are shown in the same colour. Human equivalents of the mouse


lymphoid stem cell
pro-B-cell (progenitor)
pre-B cell
immature B cell
mature B cell
activated/blast B cell
memory B cell
plasma cell (AFC)
Ig gene rearrangement
antigen
markers
cytoplasmic μ+
surface IgM+
surface IgM+, IgD+
surface IgM+, IgD−
surface IgG+/IgA+
cytoplasmic Ig+
Tdt
MHC II
CD10
CD19
CD20
CD21
CD22
CD23
CD25
CD38
CD72
PCA-1
B-cell differentiation

2. B Cell Subsets

B-1: CD5+, mIgM+
B-2: CD5-, mIgD+

COMPARISON OF PROPERTIES OF $CD5^+$ B CELLS AND CONVENTIONAL B CELLS

Properties	$CD5^+$ B cells	Conventional
Ontogeny	Early	Late
Renewal	Self Renewal	Replaced from bone marrow
Production of Immunoglobulin	High	Low
Isotypes secreted	IgM>>IgG	IgG>IgM
Bind multiple different ligands	Yes	No

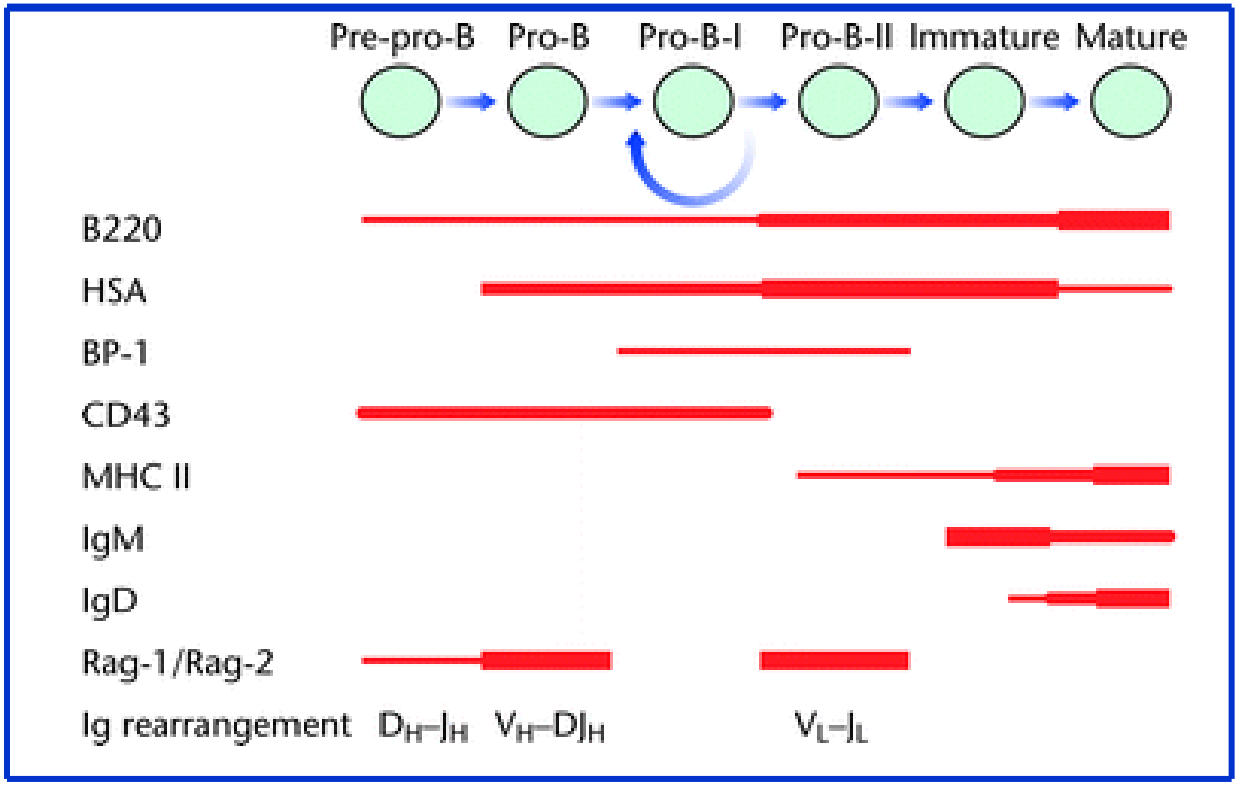
Adapted from Janeway and Travers, Immunobiology

B1a,B1b和B2细胞亚群的表型

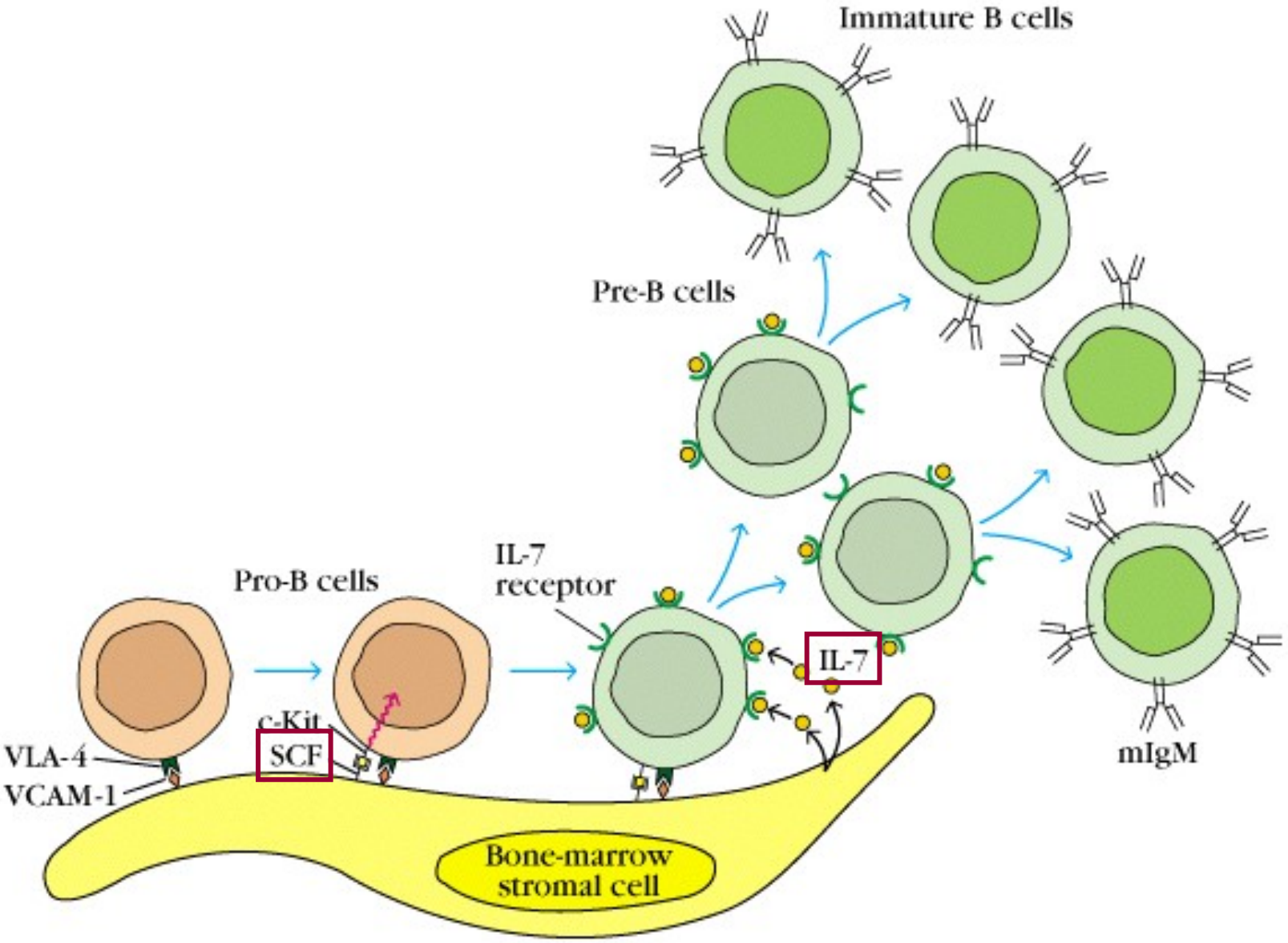
表面标记	B1a	B1b	B2
IgM	+++	+++	+
IgD	+/-	+/-	+++
CD5	+	-	-
CD11	+	+	-
CD23	-	-	+
CD44	+	+	-
MHCⅡ	+++	+++	++

3. The Development of B Lymphocytes

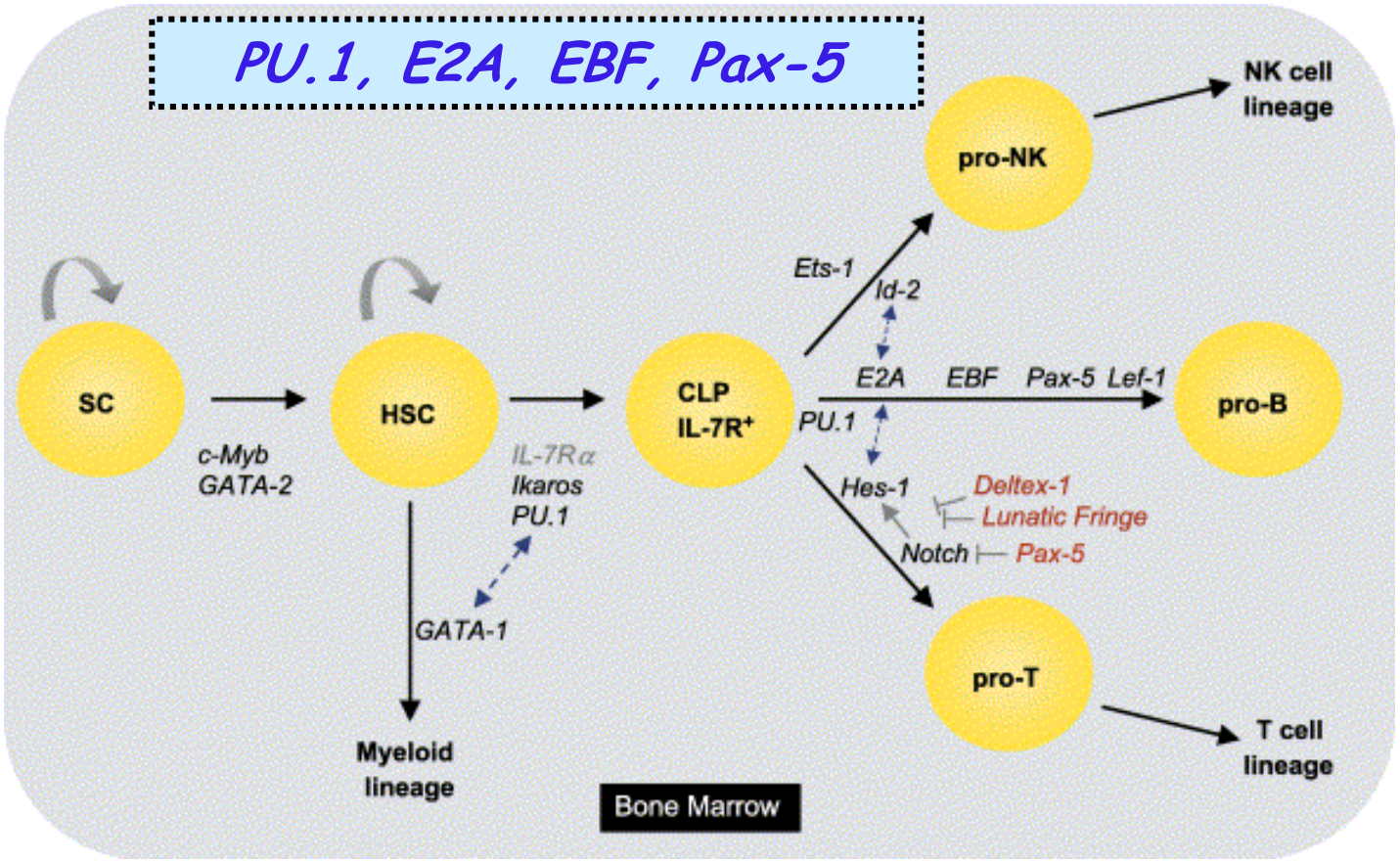
early-pro B cell: rearrangement of D-J gene
late-pro B cell: rearrangement of V-DJ gene
large-pre B cell: express μ : λ5/VpreB
small-pre B cell: express μ , rearrangement of V-J gene
immature B cell: express mIgM
mature B cell: express mIgM, mIgD



B-Cell Development in the Bone Marrow



Transcriptional control of B cell development and function



Lineage commitment in the bone marrow. The position of the transcription factors on the scheme represents the stage at which their absence (based usually on knockout studies) leads to a developmental block. Proteins normally acting as inhibitors of the differentiation pathways are depicted in red. Physical interactions between transcription factors are indicated by double-pointed blue arrows. SC, stem cell; HSC, hematopoietic stem cell; CLP, common lymphoid progenitor; Gene. 2004 Feb 18;327(1):1-23

PU.1, E2A, EBF1, Pax-5

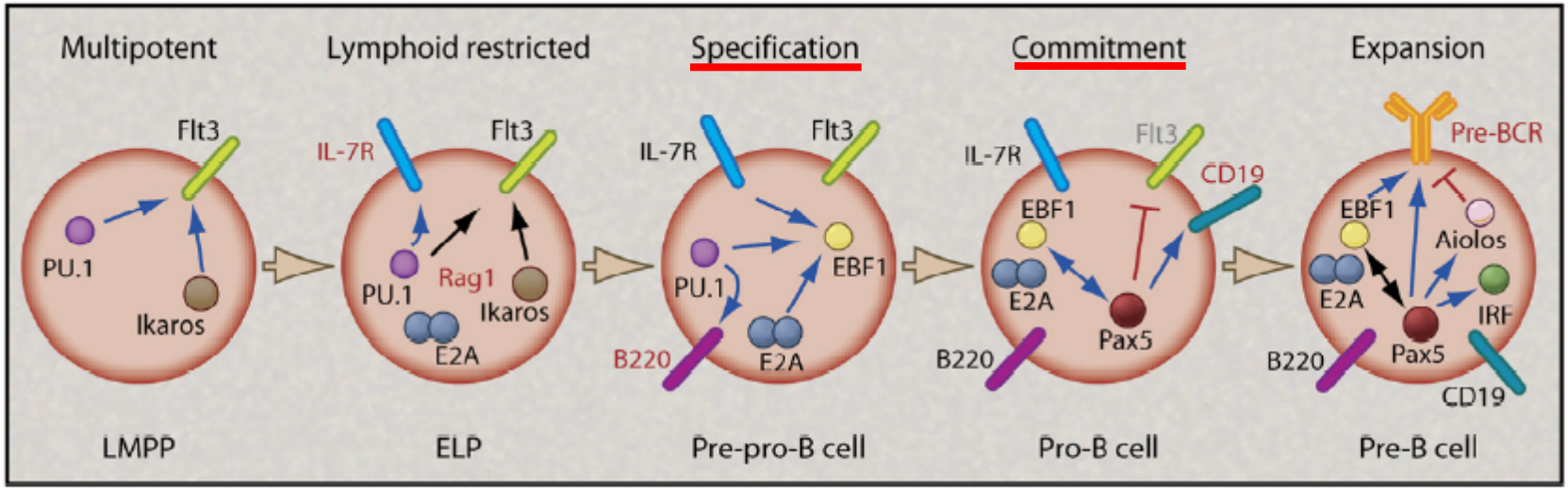


Figure 1. Multistep Model of B Cell Development

Successive stages of differentiation from the LMPP (lymphoid-primed multipotent progenitor), ELP (early lymphoid progenitor), pre-pro-B cell, and committed pro- and pre-B cell are depicted. Developmental capacities of the successive stages are indicated. Key transcription factors, growth-factor receptors, and cell-surface markers are shown, with important events initiated at a particular stage shown in blue. An arrow pointing upward indicates positive interactions, and ⊥ indicates gene repression. RAG1 expression is initiated in the ELP and is maintained until throughout the remaining stages depicted. IRFs, interferon regulatory factor-4 and -8; and preBCR, pre-B cell receptor.

Immunity 26:719, June 2007

B Young Again

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DOI 10.1016/j.immuni.2008.04.004

Hanna et al. (2008) report in a recent issue of *Cell* that a defined set of transcription factors can reprogram mature B cells back to pluripotent stem cells.

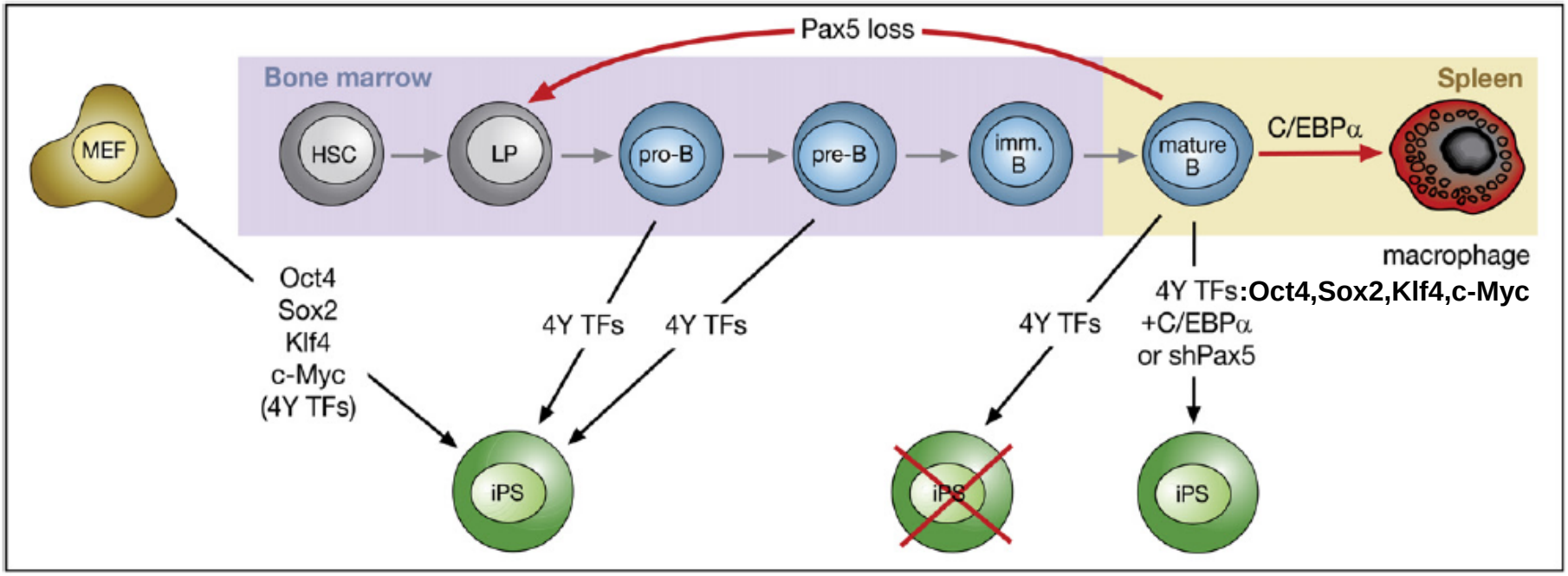
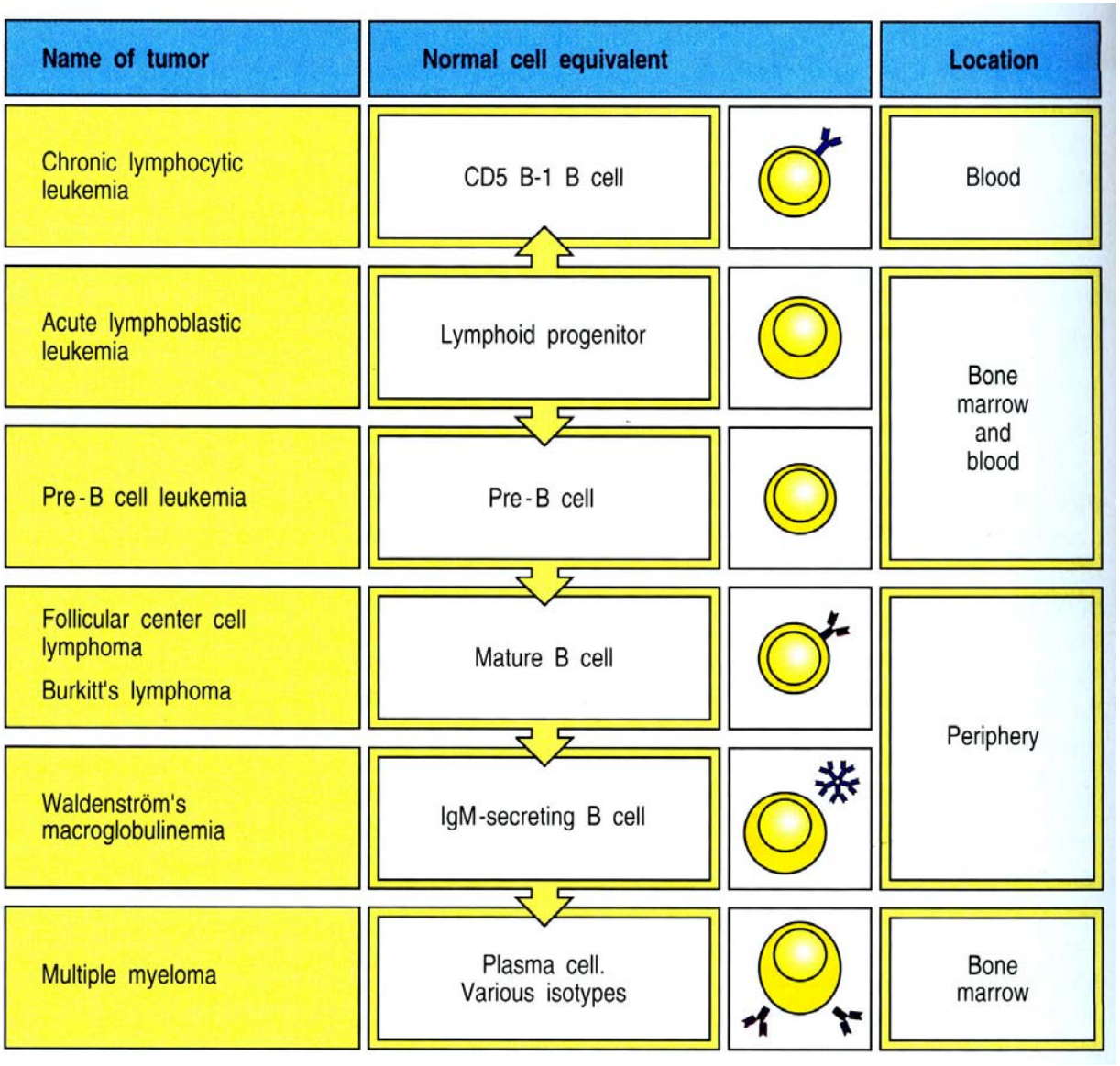


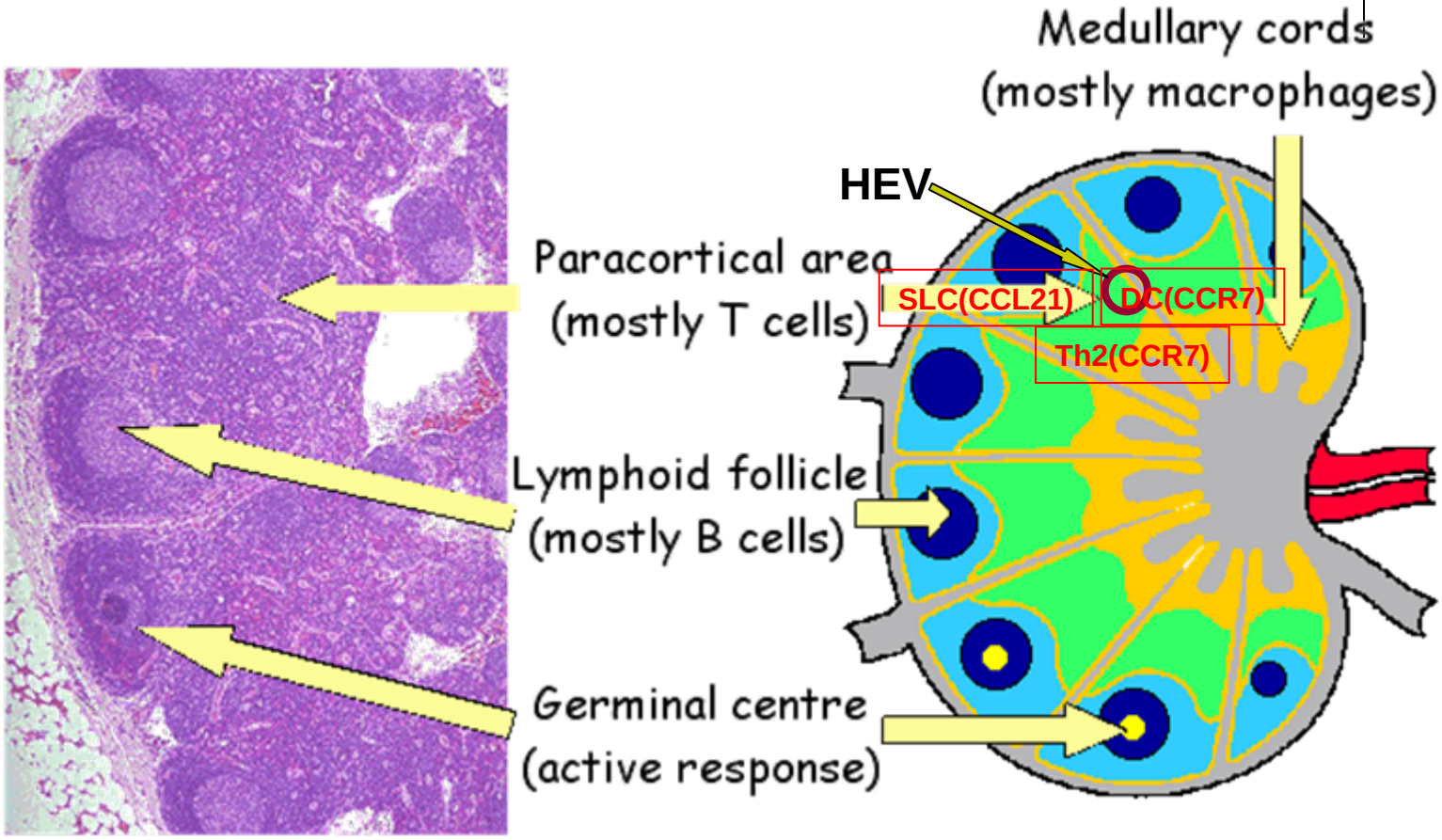
Figure 1. Reprogramming of B Lymphocytes into iPS Cells

Previous experiments demonstrated that viral expression of Oct4, Sox2, Klf4, and c-Myc (4 Yamanaka transcription factors; 4Y TFs) in mouse embryo fibroblasts (MEFs) induces the formation of induced pluripotent stem (iPS) cells (black arrow). It was also shown that forced expression of C/EBPα in mature B cells induces their transdifferentiation into macrophages via inhibition of Pax5 function and upregulation of PU.1 expression (red arrow). Furthermore, conditional *Pax5* inactivation was shown to allow mature B cells to dedifferentiate into uncommitted lymphoid progenitors (LP, red arrow). The work of Hanna et al. (2008) now demonstrates that the 4Y TFs induce iPS cell formation in pro-B cells and pre-B cells, whereas these factors are ineffective in mature B cells. Mature B cells are only induced to develop into iPS cells upon coexpression, with the 4Y TFs, of either C/EBPα or an shRNA lentivirus interfering with *Pax5* expression (shPax5). Hematopoietic stem cells, HSC.

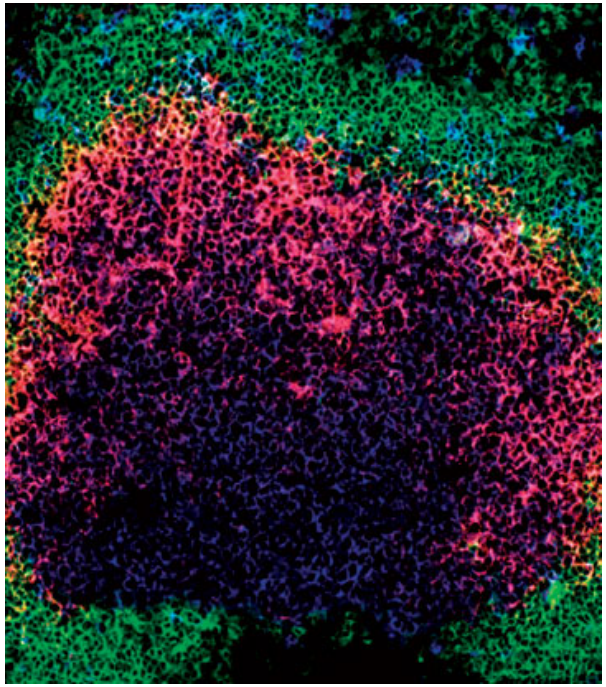
4. B-cell Tumor



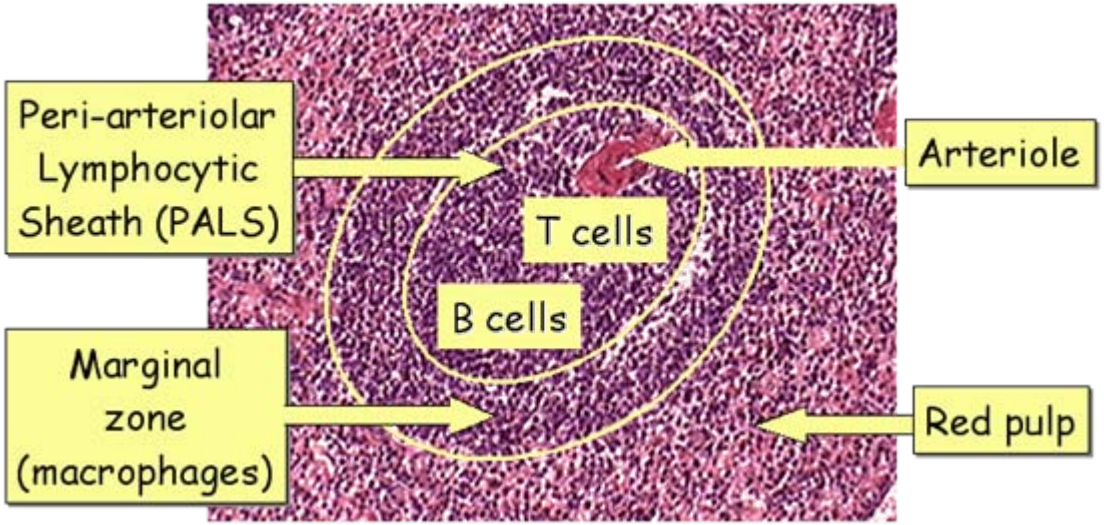
5. Activation of B cell proliferation



B cell maturation in the lymph node

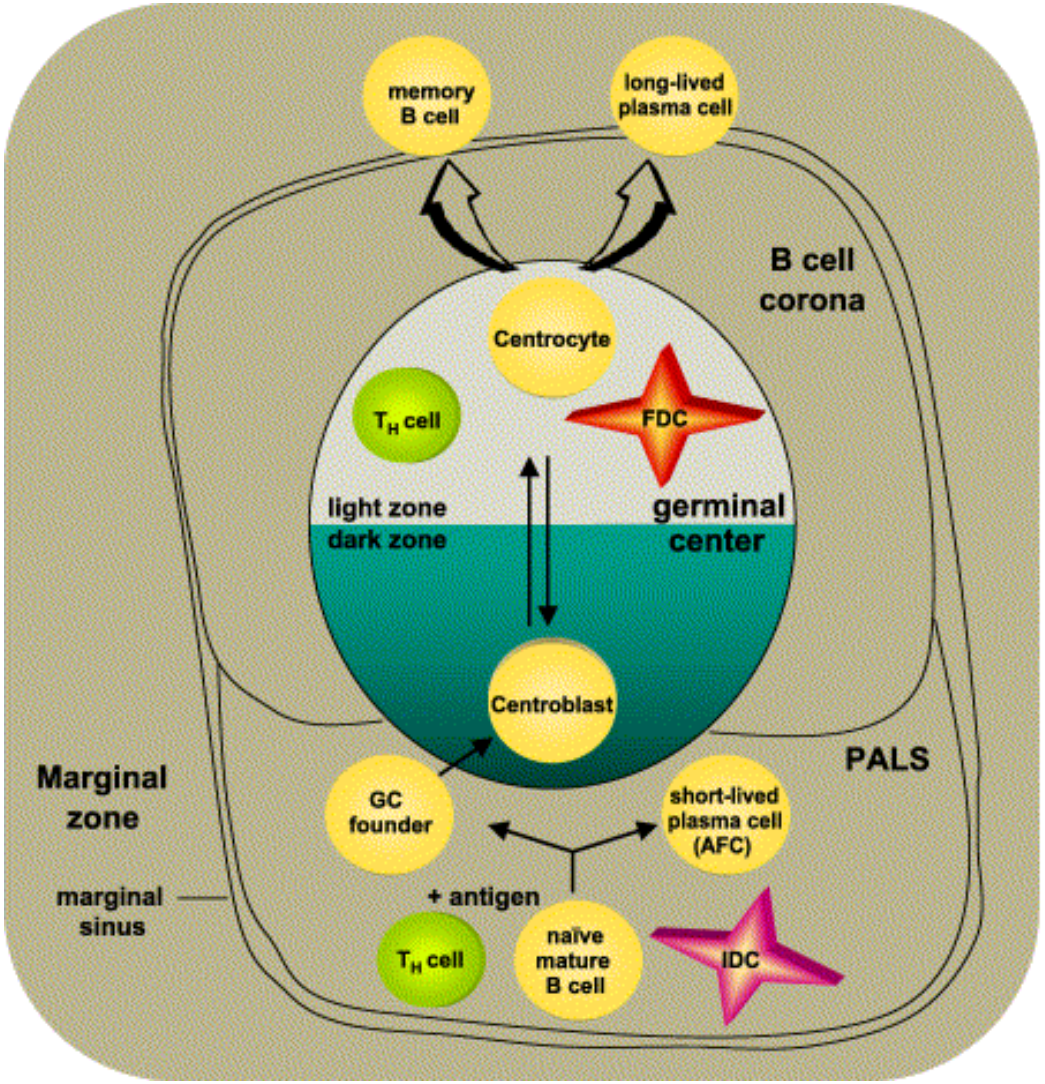


NAT REV IMMUNOL
July 2007 Vol 7 No 7



B cell maturation in the spleen

B cell maturation in the spleen



Ag-dependent T cell-mediated selection and diversification (class switch recombination, apoptosis of self-reactive B cells, terminal differentiation into plasma cells or memory B cells)

↑

Ag-dependent selection of high-affinity BCR-bearing B cells by FDCs, apoptosis of low-affinity B cells

↑

Proliferation and diversification of centroblasts by somatic hypermutation

↑

B cells differentiate either in low-affinity AFCs or initiate the GC reaction

↑

Ag-dependent B cell activation by T cells primed by interdigitating cells

Gene. 2004 Feb 18;327(1):1-23

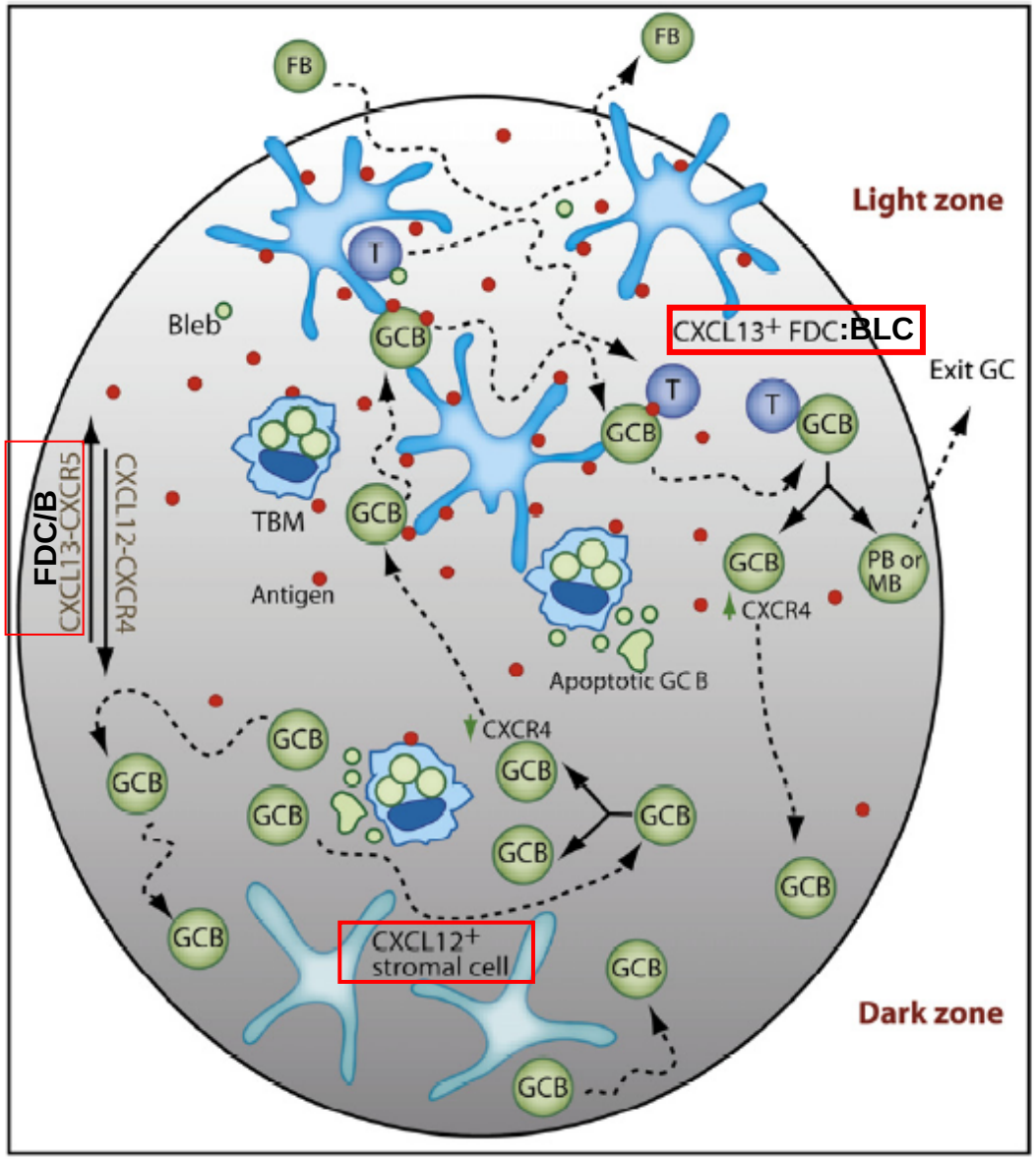
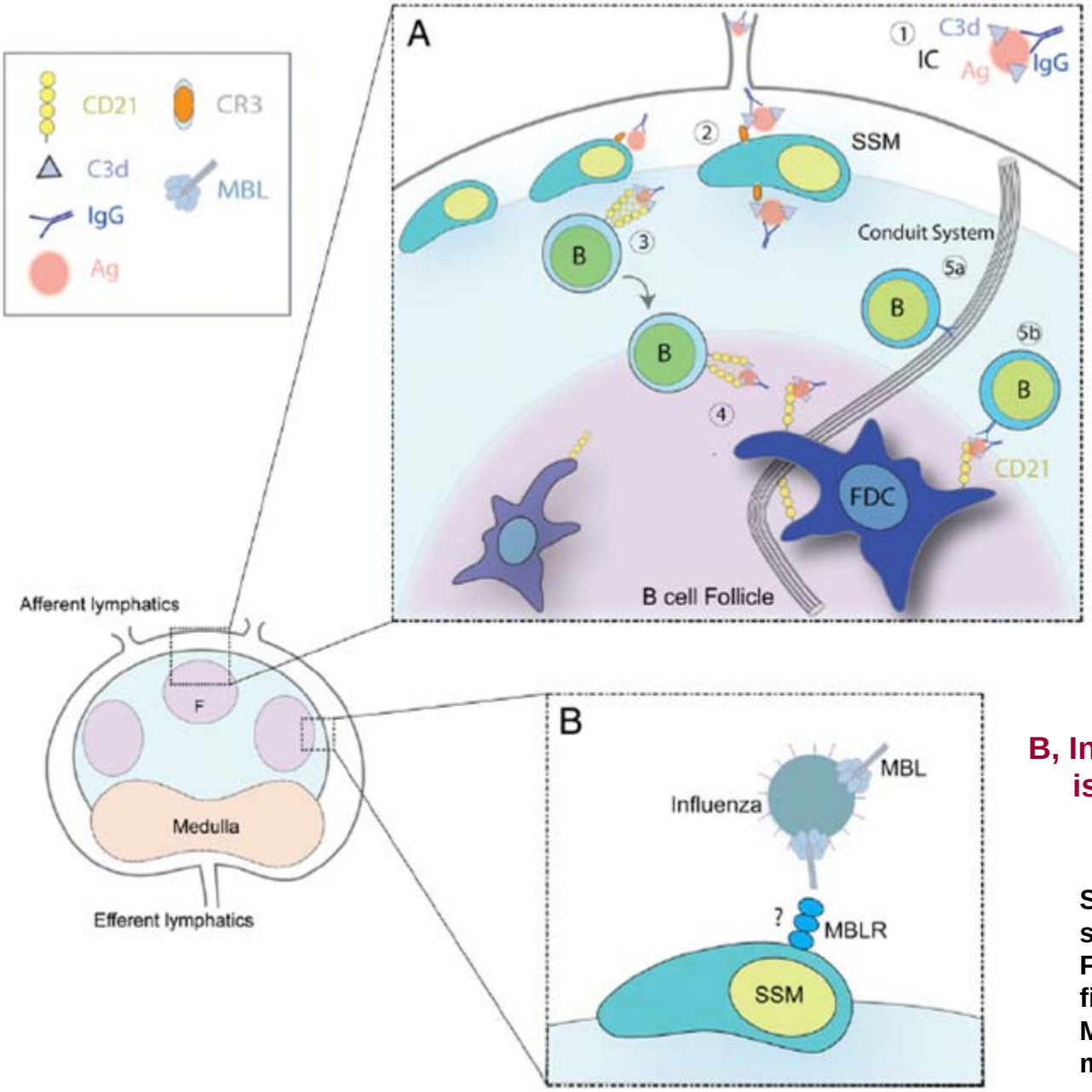


Figure 1. Schematic Representation of GC Compartments and Cellular Dynamics

Diagram depicts the structure of an acute GC. Chronic GCs such as those typical of tonsils might have additional compartmentalization. The light zone is composed of CXCR4^{lo} GC B cells, a dense network of CXCL13^{+} FDCs, CXCR5^{hi} GC T cells, and tingible-body macrophages (TBM). The dark zone is composed of CXCR4^{hi} GC B cells, a sparse network of CXCL12^{+} stromal cells, tingible-body macrophages, and some GC T cells. Dark- and light-zone GC B cells are medium-sized blasts expressing low surface Ig and exhibiting a dendritic morphology. Additional cell types might sometimes be present, including dendritic cells (Grouard et al., 1996) and CD4^{+}CD3^{-} cells (Kim et al., 2003). GC B cells migrate extensively within their respective compartments and move between compartments, most likely after modulating CXCR4 protein levels. Cell division and cell death can occur in both zones. Blebs of apoptotic GC B cells can associate with T cells, possibly limiting the availability of T cell help. Antigen is displayed as immune complexes (ICs) on FDCs but also possibly on tingible-body macrophages and motile B cells. Soluble antigen might also be present. Follicular B cells can access the light zone and might contribute to the ongoing delivery of ICs or might sometimes join the GC response. The following abbreviations are used: GC B cell (GCB), plasmablast (PB), and memory B cell (MB).



A, Pathways for the circulation of Ag in the LN.

1, Complement C3 opsonizes Ag in the presence of Ab. C3-ICs are formed by the deposition of complement proteins and IgG on the surface of the Ag.

2, The retention of C3-ICs on the surface of the SSMs is CR3 and FcRIIb dependent.

3, B cells transport C3-ICs from the surface of the SSMs to the FDCs in a CD21-dependent manner.

4, C3-ICs are transferred to FDCs.

5a, Cognate B cells acquire small Ag drained via FRC conduits directly or

(5b) from the FDC surface.

B, Influenza virus uptake by SSMs is MBL dependent.

SSM,
subcapsular sinus-lining macrophage;
FRC,
fibroblast reticular cell;
MBL,
mannose-binding lectins.

The Journal of Immunology, 2010, 185:2659–2664.

Key B cell decisions after antigen exposure

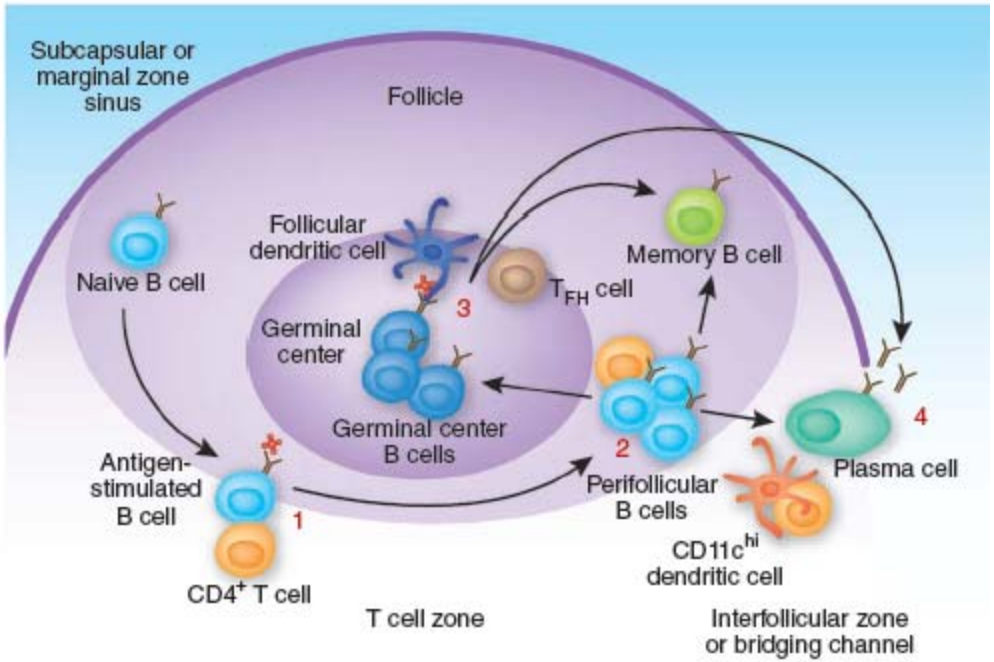


Figure 1 Key B cell decisions after antigen exposure. (1) Within hours, binding of antigen to the BCR triggers B cell movement to the interface between the follicle and T cell zone, where B cells present antigen peptides to $CD4^+$ T cells. At this point the B cells (and T cells) integrate inputs to decide between death or proliferation. During the next 2–3 days, the B cells migrate actively, form repeated stable conjugates with $CD4^+$ T cells and proliferate at the periphery of the follicle, particularly near the interfollicular zones and bridging channels rich in $CD11c^{hi}$ dendritic cells. (2) Three to four days after antigen exposure, the B cells integrate inputs to decide between differentiation into plasma cells, GC B cells or memory B cells. GC B cells continue dividing rapidly, hypermutate their BCR V-regions and interact with follicular dendritic cells bearing antigen and T follicular helper cells (T_{FH} cells). (3) GC B cells integrate inputs to decide between survival or death depending on their BCR affinity for foreign and self antigens. (4) Plasma cells integrate inputs to decide between survival or death to determine the quantity and duration of antibody in the circulation.

Nature immunology, 2010; 11(8): **682**

Positive affinity selection

Negative affinity selection

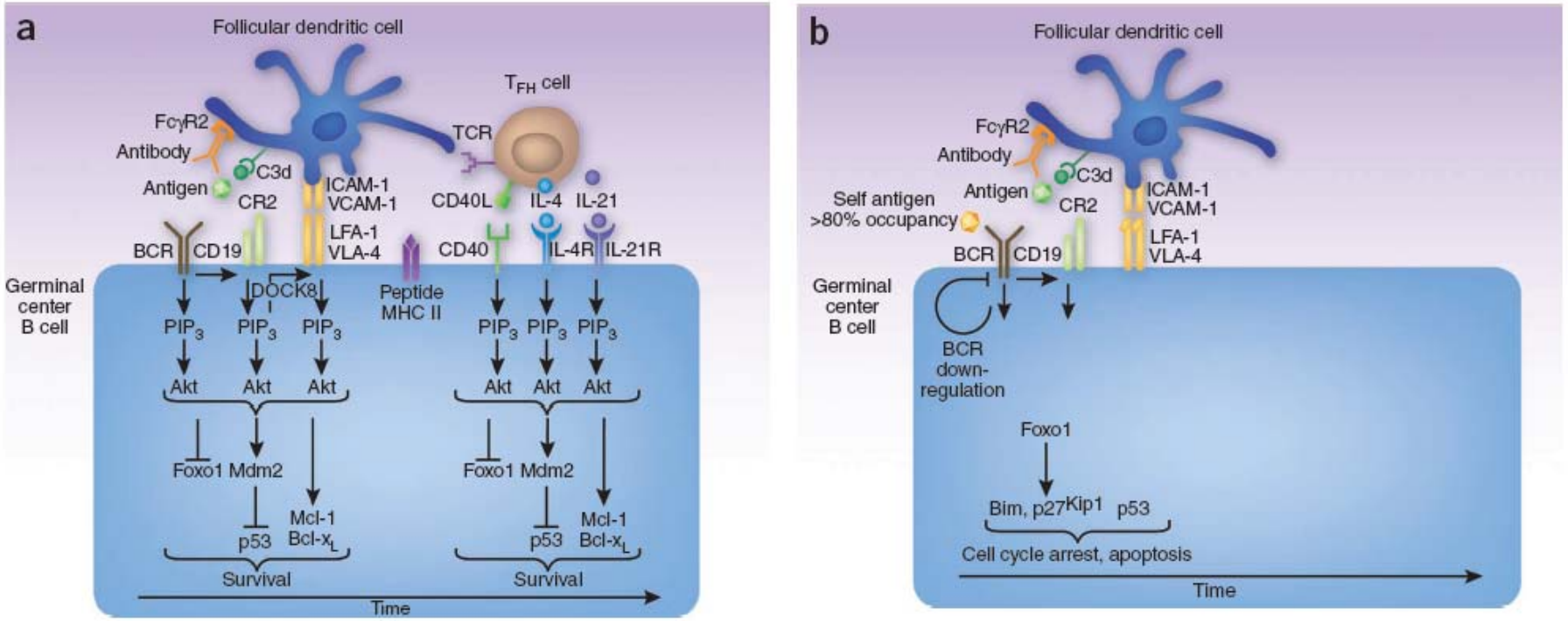
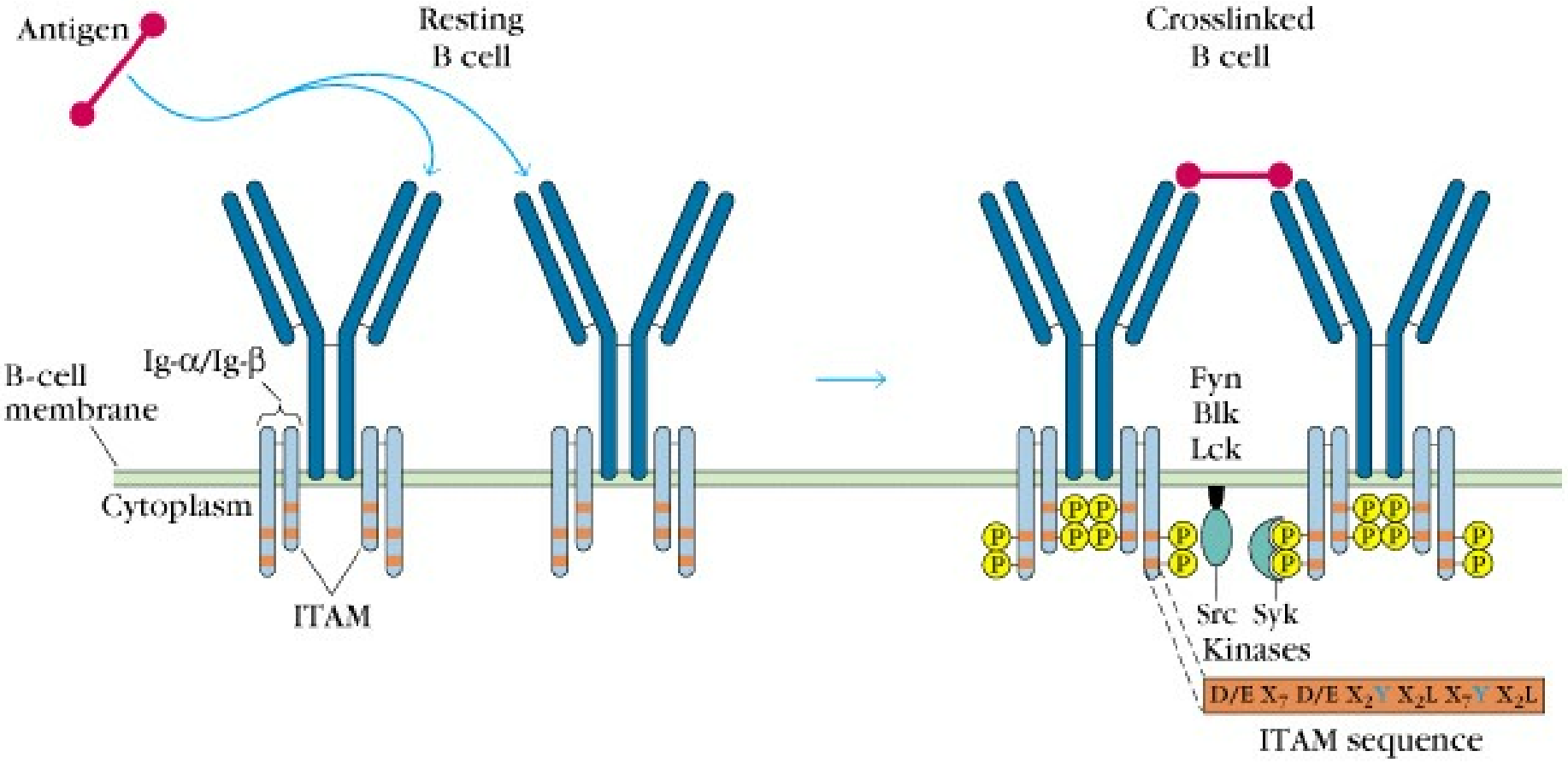
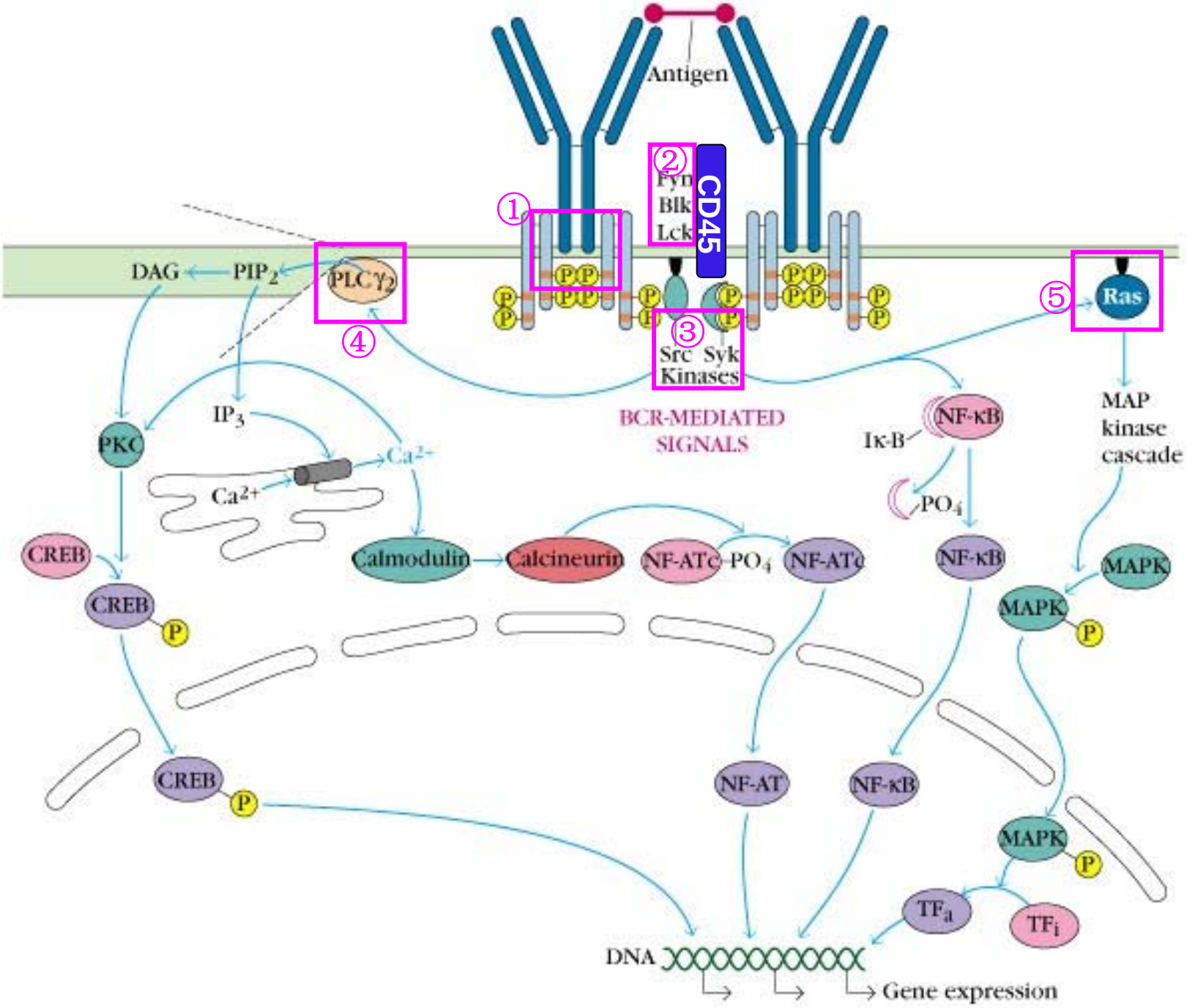


Figure 2 Proposed mechanism for concurrent positive and negative affinity selection of GC B cells. (**a**) Positive affinity selection. Foreign antigen is displayed in small amounts on FDCs bound with complement C3d or as immune complexes bound to FcγR2. A small percentage of the high-affinity BCRs on the GC B cell bind antigen and activate PI(3)K—directly and through CD19, the latter augmented by complement receptor 2 (CR2) binding to C3d. PIP_3 recruits DOCK8 for inside-out signaling, increasing avidity of integrins LFA-1 and VLA-4 for ICAM-1 and VCAM-1. Integrin outside-in signaling cooperates with BCR and CD19 signaling to sustain PIP_3 production and Akt activation, preventing accumulation of the proapoptotic and antiproliferative proteins p53, Bim and $p27^{Kip1}$; inducing expression of the antiapoptotic proteins Mcl-1 and Bcl-x_L; and promoting short-term GC B cell survival. Signaling will be cut short if antigen is displaced from the BCR by competing antibodies or other B cells, or by mutations in CD19 or DOCK8. Subsequent presentation of peptide–MHC class II to T_{FH} cells elicits CD40L, IL-4 and IL-21, promoting longer-term survival of the GC B cell. (**b**) Negative affinity selection. The majority of BCRs are engaged simultaneously by self antigen, causing intracellular signaling events that downregulate surface BCRs. Without sufficient surface BCRs, PIP_3 production ceases, resulting in the accumulation of growth-arrest and proapoptotic proteins.

Nature immunology, 2010; 11(8): **683**

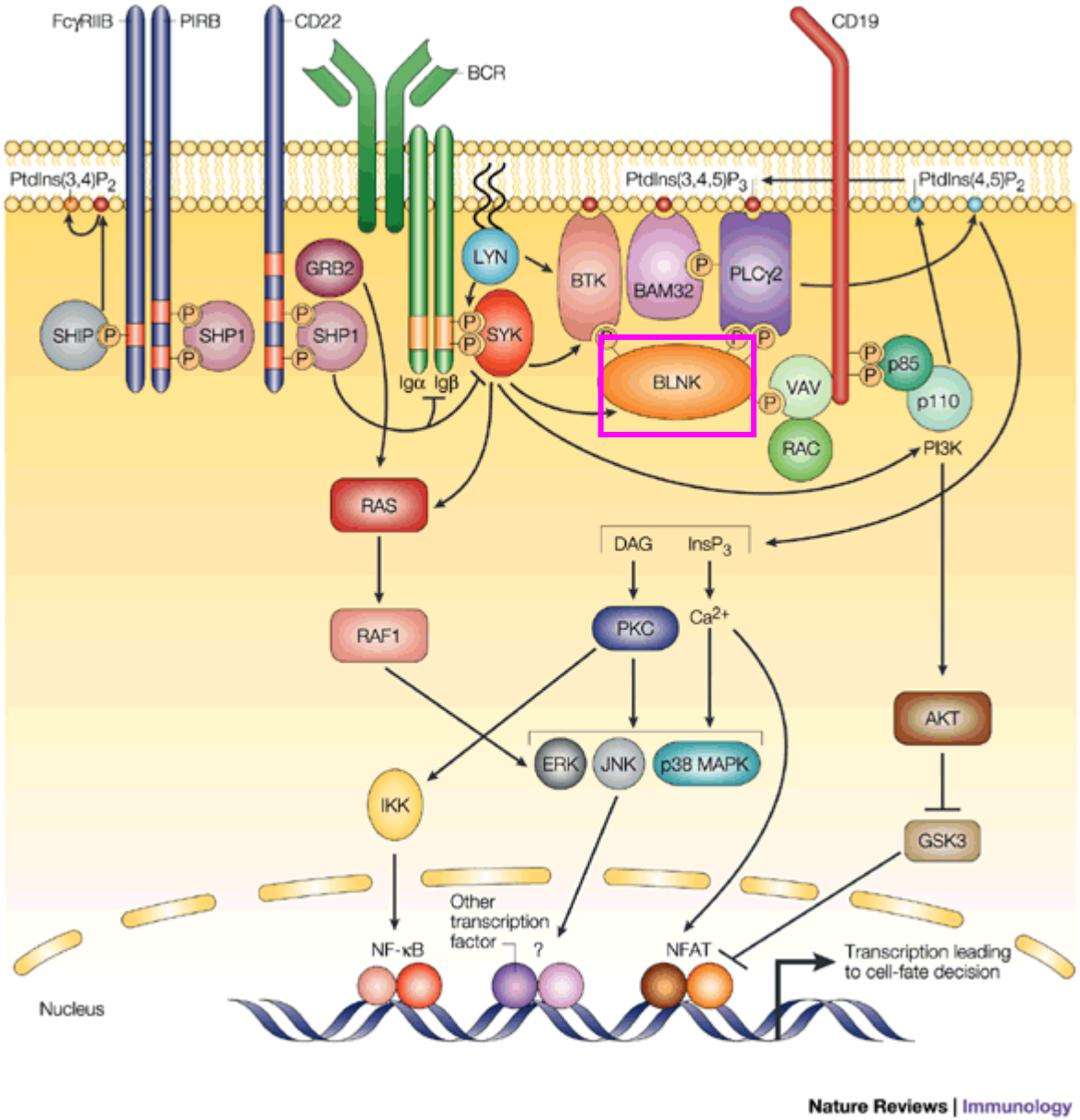
6. B cell signal transduction




Antigen
①
②
Fyn
Blk
Lck
CD45
③
Src Syk
Kinases
④
PLCγ2
DAG
PIP2
IP3
PKC
Ca2+
Ca2+
⑤
Ras
BCR-MEDIATED
SIGNALS
NF-κB
Iκ-B
PO4
MAP
kinase
cascade
CREB
CREB
P
Calmodulin
Calcineurin
NF-ATc
PO4
NF-ATc
NF-κB
MAPK
MAPK
P
CREB
P
NF-AT
NF-κB
MAPK
P
TFa
TFi
DNA
Gene expression

Nature Reviews Immunology **2**; 945-956 (2002);

REGULATION OF B-CELL FATE BY ANTIGEN-RECEPTOR SIGNALS



BCR-induced signal-transduction pathways.

BCR-induced signal-transduction pathways. After antigen ligation, three main protein tyrosine kinases (PTKs) — the SRC-family kinase LYN, SYK and the TEC-family kinase BTK — are activated. Phosphatidylinositol 3-kinase (PI3K) and phospholipase C 2 (PLC 2) are important downstream effectors of B-cell receptor (BCR) signalling. B-cell adaptors, such as B-cell linker (BLNK) and BAM32 (B-lymphocyte adaptor molecule of 32 kDa), fine-tune BCR signals by efficiently connecting the kinases with the effectors. A PI3K product, phosphatidylinositol-3,4,5-trisphosphate (PtdInsP3), recruits some BCR signalling components through their pleckstrin-homology domains, and also activates downstream kinases such as AKT. Activation of PLC 2 leads to the release of intracellular Ca2+ and activation of protein kinase C (PKC) — both of which are crucial for the activation of mitogen-activated protein kinases (MAPKs), such as extracellular signal-regulated kinase (ERK), c-JUN NH2-terminal kinase (JNK) and p38 MAPK, and transcription factors, including nuclear factor- B (NF- B) and nuclear factor of activated T cells (NFAT). The profiles of these outputs determine B-cell fate. DAG, diacylglycerol; Fc RIIB, low-affinity Fc receptor for IgG; GSK3, glycogen synthase kinase 3; IKK, inhibitor of NF- B (I B) kinase; PIRB, paired immunoglobulin-like receptor B; SHIP, SH2-domain-containing inositol polyphosphate 5' phosphatase; SHP1, SH2-domain-containing protein tyrosine phosphatase 1. ……

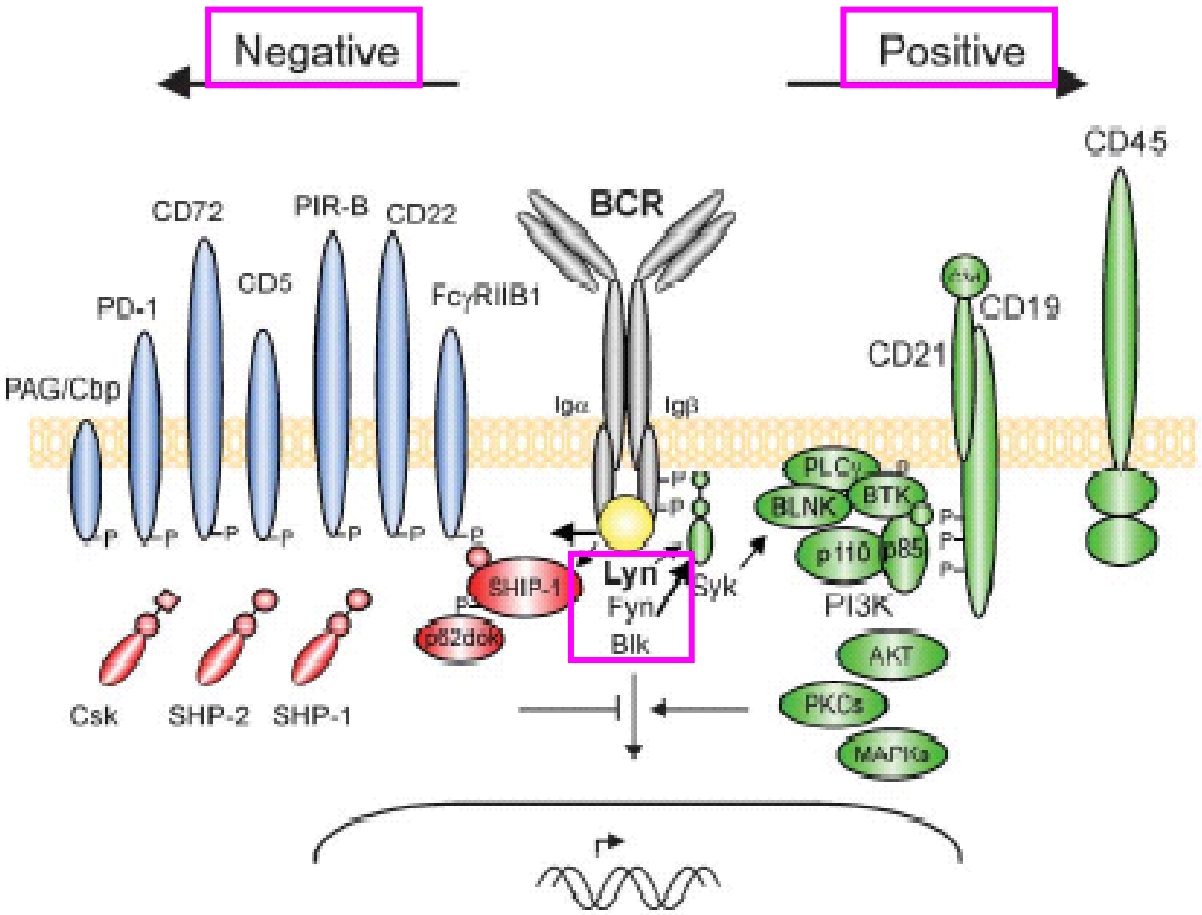
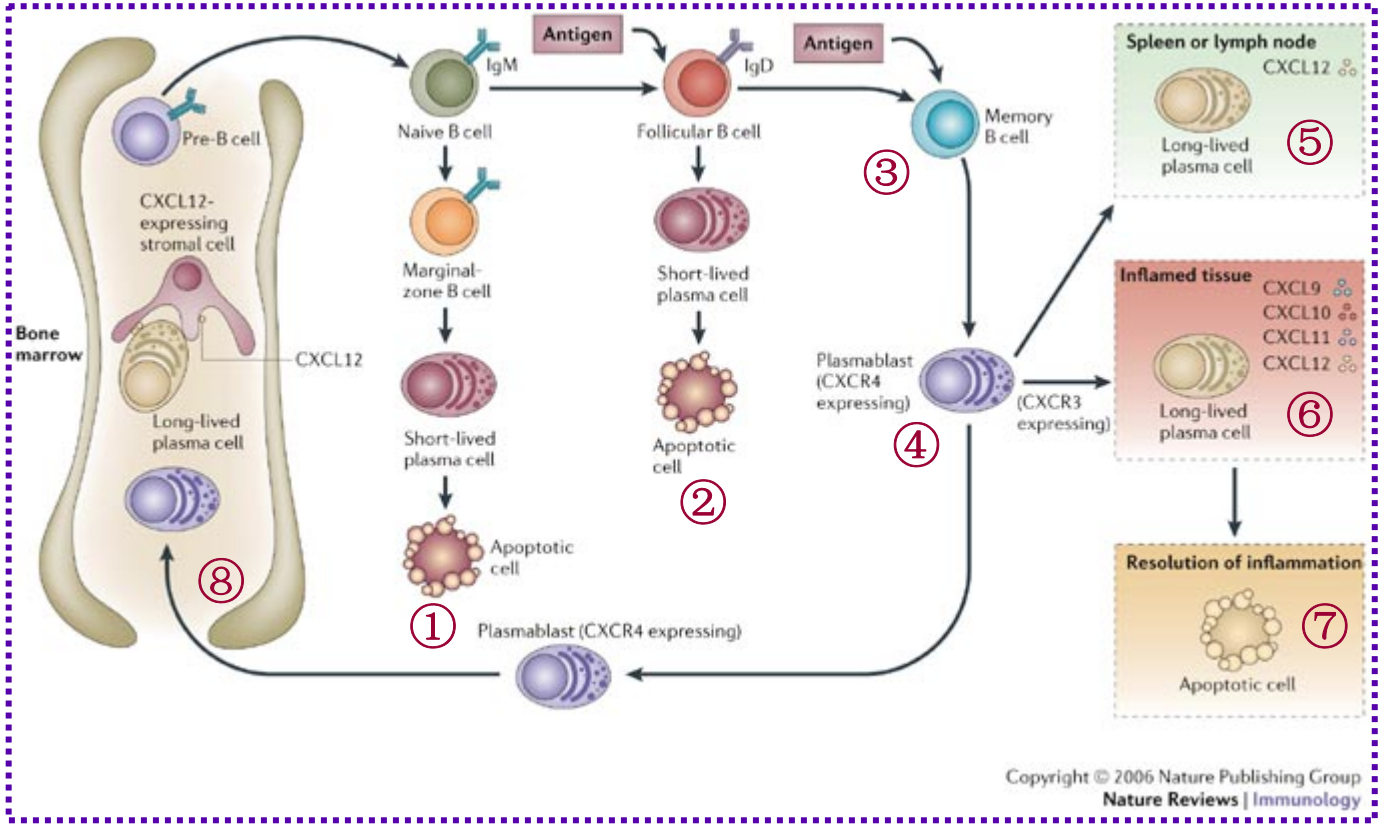


Figure 3. Schematic Representation of Signal Transduction Pathways Modulated by Lyn in B Cells

Lyn contributes to positive regulation of signaling through tyrosine phosphorylation of ITAMs in the Igα and Igβ components of the BCR and in CD19. This role can be assumed by other SFKs such as Fyn and Blk, and promotes B cell activation through the recruitment of Syk and PI3K. Lyn plays an essential role in negative regulation of signaling through its unique ability to phosphorylate ITIMs in inhibitory cell surface receptors such as FcγRIIb1, CD22, PIR-B, and CD5 and a potential inhibitory site on Syk (see text). Whether CD72, PAG, and PD-1 are Lyn targets in vivo has yet to be confirmed. Positive phosphorylation of Syk is redundant with other SFKs. ITIM phosphorylation induces the recruitment of inhibitory phosphatases such as SHP-1/2 and SHIP-1, which down modulate signaling. Lyn is also suspected to be critical for the phosphorylation of PAG/Cpb in B cells, thereby enabling Csk recruitment to the plasma membrane where it may modulate SFK activity. Squares, SH3 domains; circles, SH2 domains; and –P, phospho tyrosines. The single –P on each inhibitory receptor is indicative and not a representation of the true target number.

7. Ontogeny of plasma cells



Andreas Radbruch, …..Nature Reviews Immunology 6, 741-750 (October 2006)

The heritage and the dynamics of plasma-cell life in humoral immune responses are shown. B cells that are generated in the bone marrow exit as precursor B cells (pre-B cells), which are immature and express IgM. These cells further mature into naive B cells and then into either marginal-zone B cells or follicular B cells. When activated, these marginal-zone and follicular B cells can differentiate into plasmablasts (not shown) and short-lived plasma cells, both of which can secrete antibody. Alternatively, with the help of T helper cells, follicular B cells can also differentiate into memory B cells, which are long-lived, and express antibodies of switched class and high affinity for antigen. When reactivated by antigen, memory B cells can differentiate into plasmablasts, which are competent to become long-lived plasma cells. ①A small proportion of these plasmablasts stay in the secondary lymphoid organ (the spleen or the lymph node) where they were generated. ②Most of the plasmablasts migrate either to inflamed tissue, under the control of interferon- -induced expression of CXC-chemokine receptor 3 (CXCR3; which binds CXC-chemokine ligand 9 (CXCL9), CXCL10 and CXCL11), ③or to the bone marrow, under the control of chemotaxis towards CXCL12 (which binds CXCR4). All three tissues have finite numbers of plasma-cell survival niches. Plasmablasts that succeed in the acquisition of such a niche differentiate into plasma cells and become immobile. ④Resolution of inflamed tissue after a successful immune response terminates the survival niches in the tissue and therefore eliminates the resident plasma cells, and this is the peak of the immune response. In the bone marrow, and to a lesser degree in secondary lymphoid organs, long-lived plasma cells survive and provide humoral memory.

8. Antibody production

Claman experimentation:

T/B cooperation

Miller experimentation:

antibody production by B cell

Benacerraf experimentation:

hapten-carrier effect, H-C-E

Mitchison experimentation:

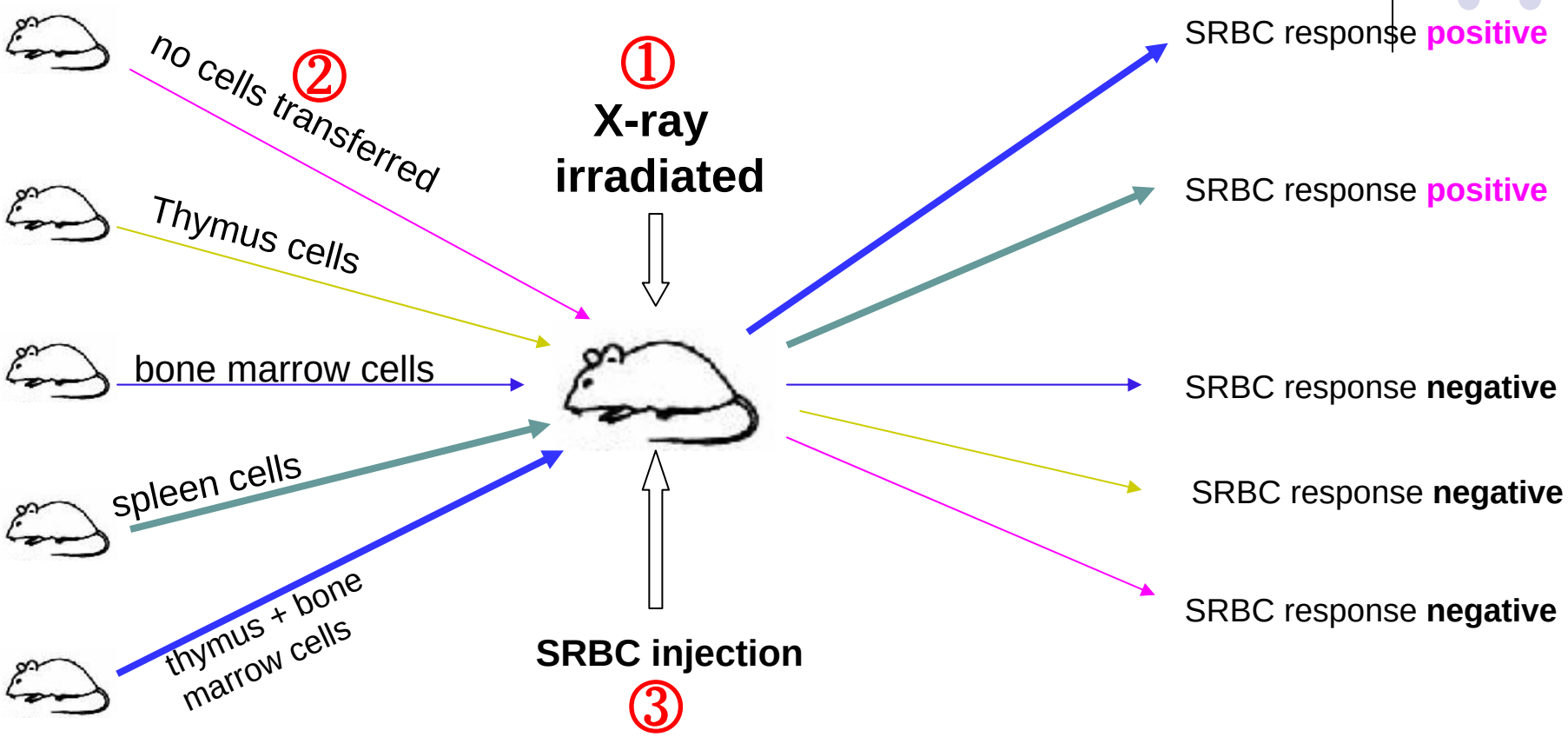
adoptive transfer carrier effect

Raff experimentation:

T cell is the carrier-reactive cell

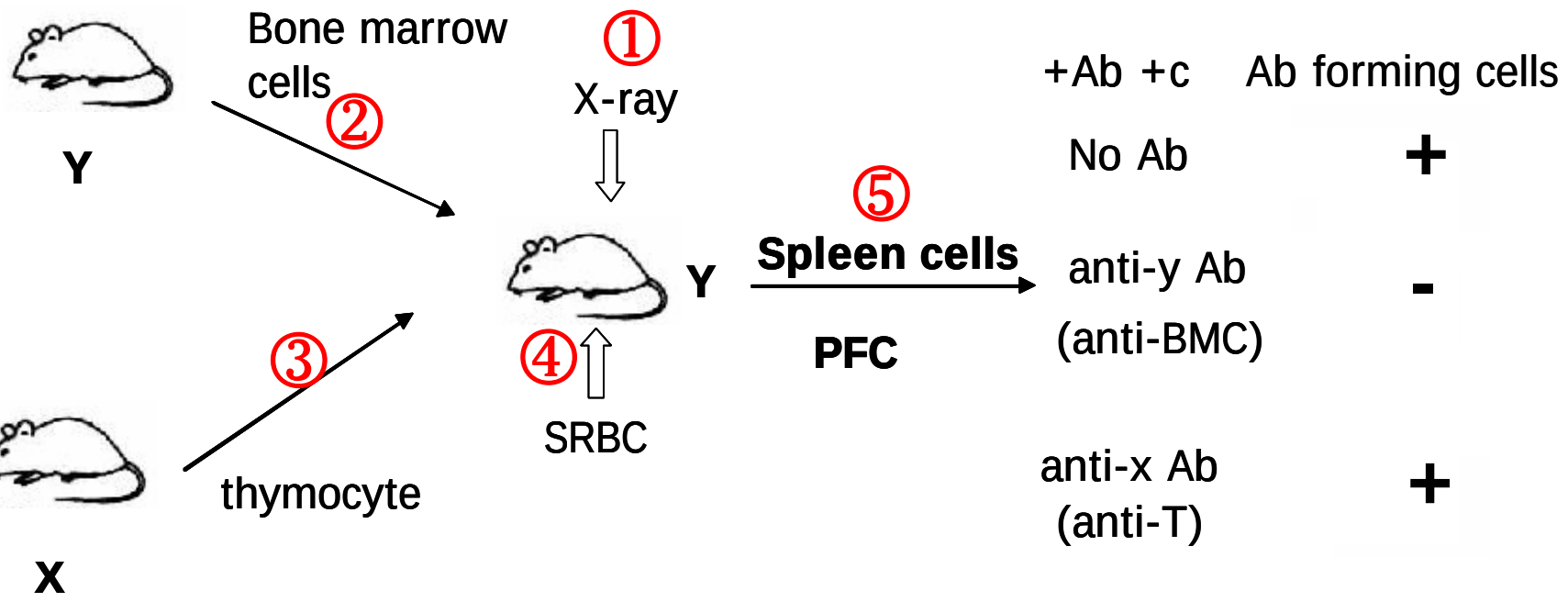
B cell is the hapten-reactive cell

Claman Experimentation(Denver,1965): T/B cooperation



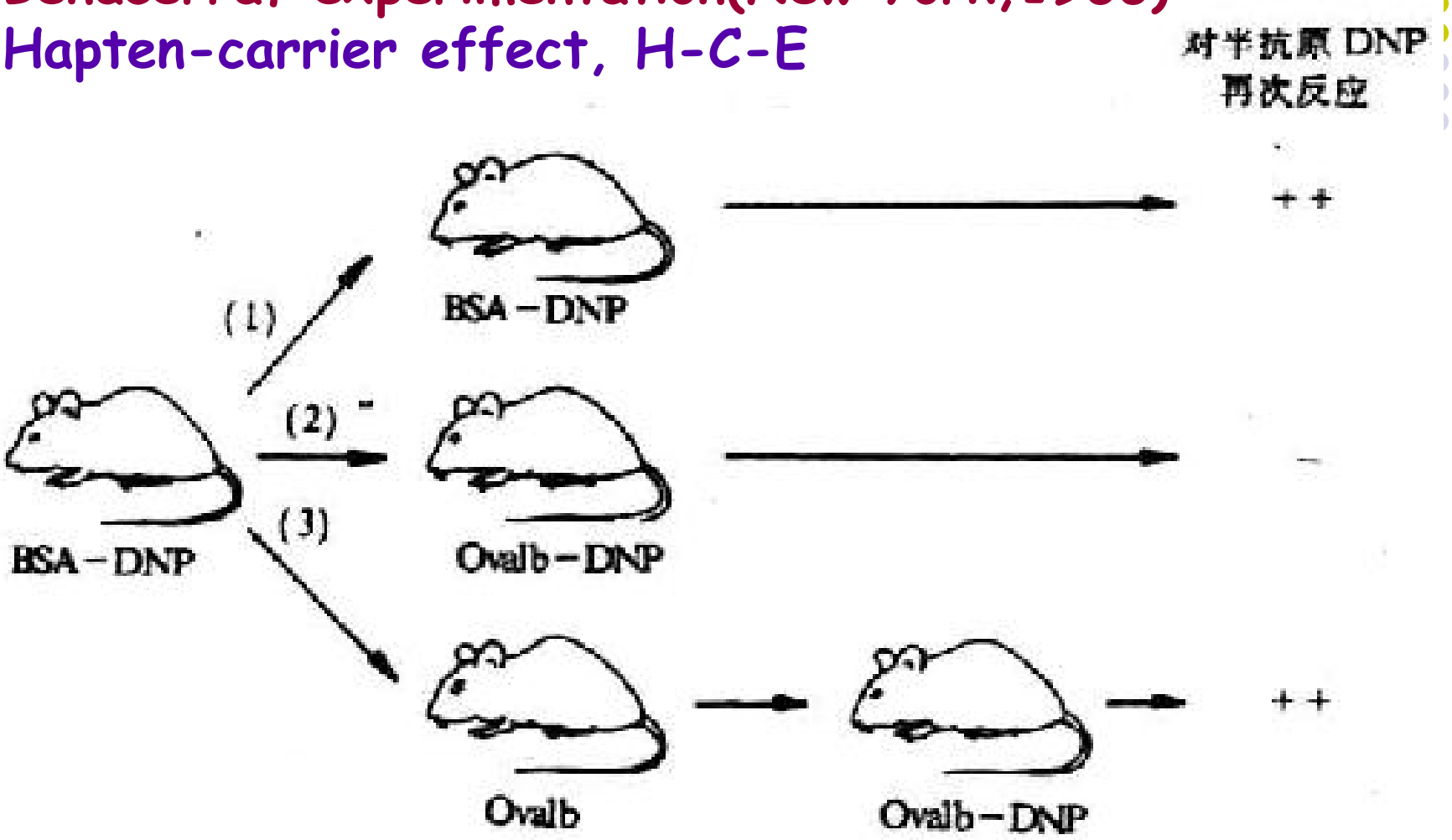
Claman, H. N., Chaperon, E. A. & Triplett, R. F. antibody production. *Proc. Soc. Exp. Biol. Med.* 122, 1167–1171 (1966)

Miller experimentation(Melbourne,1965): Antibody production by B cell



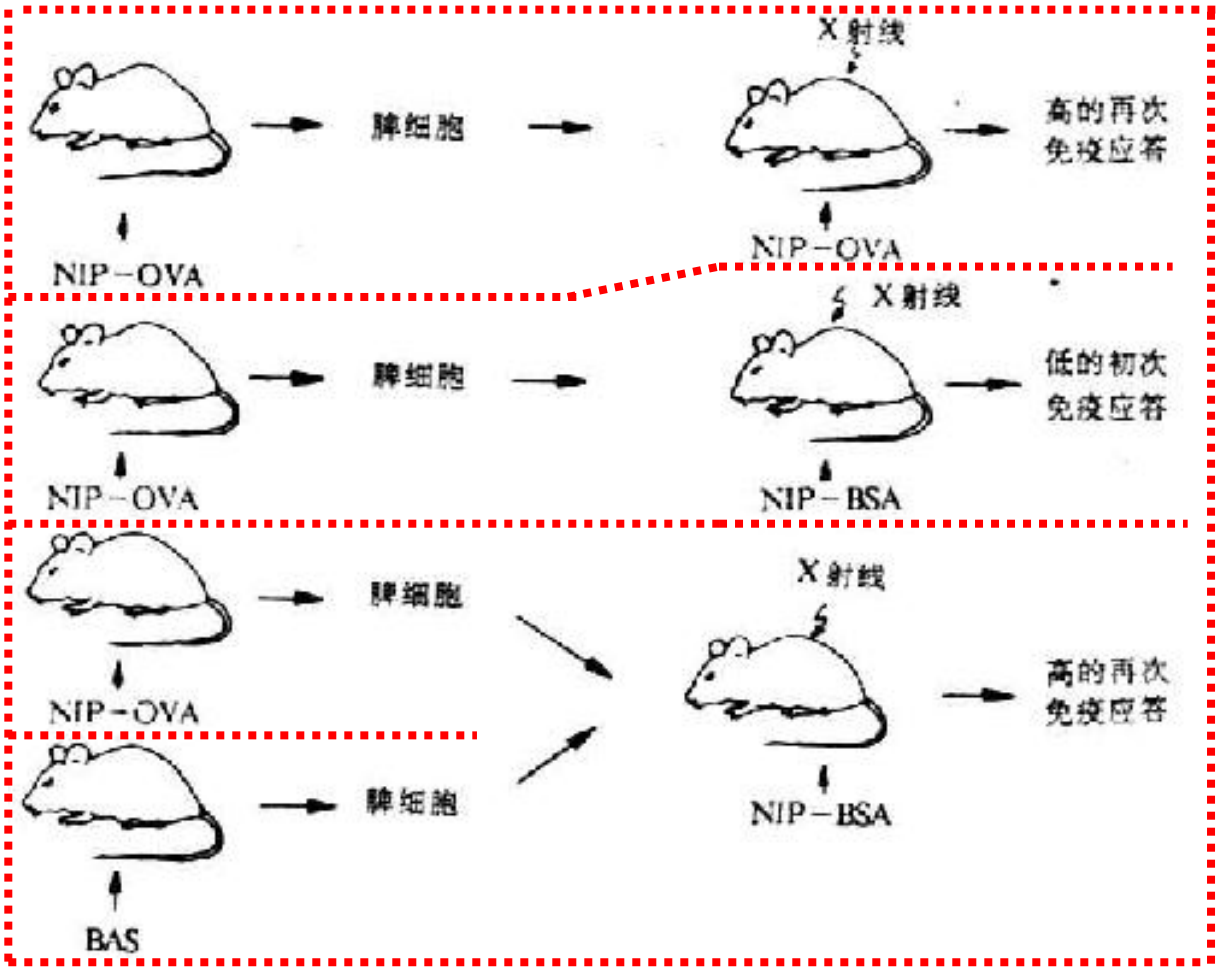
Miller, J. F., De Burgh, P. M. & Grant, G. A. Thymus and the production of antibody-plaque-forming cells. *Nature,*208, 1332–1334 (1965).

Benacerraf experimentation(New York,1966): Hapten-carrier effect, H-C-E



Paul, W. E., Siskind, G. W. & Benacerraf, B. Studies on the effect of the carrier molecule on antihapten antibody synthesis. II. Carrier specificity of anti-2,4-dinitrophenyl-poly-l-lysine antibodies. *J. Exp.Med.* 123, 689–705 (1966).

Mitchison experimentation(London and Stockholm,1967): Adoptive transfer carrie effect



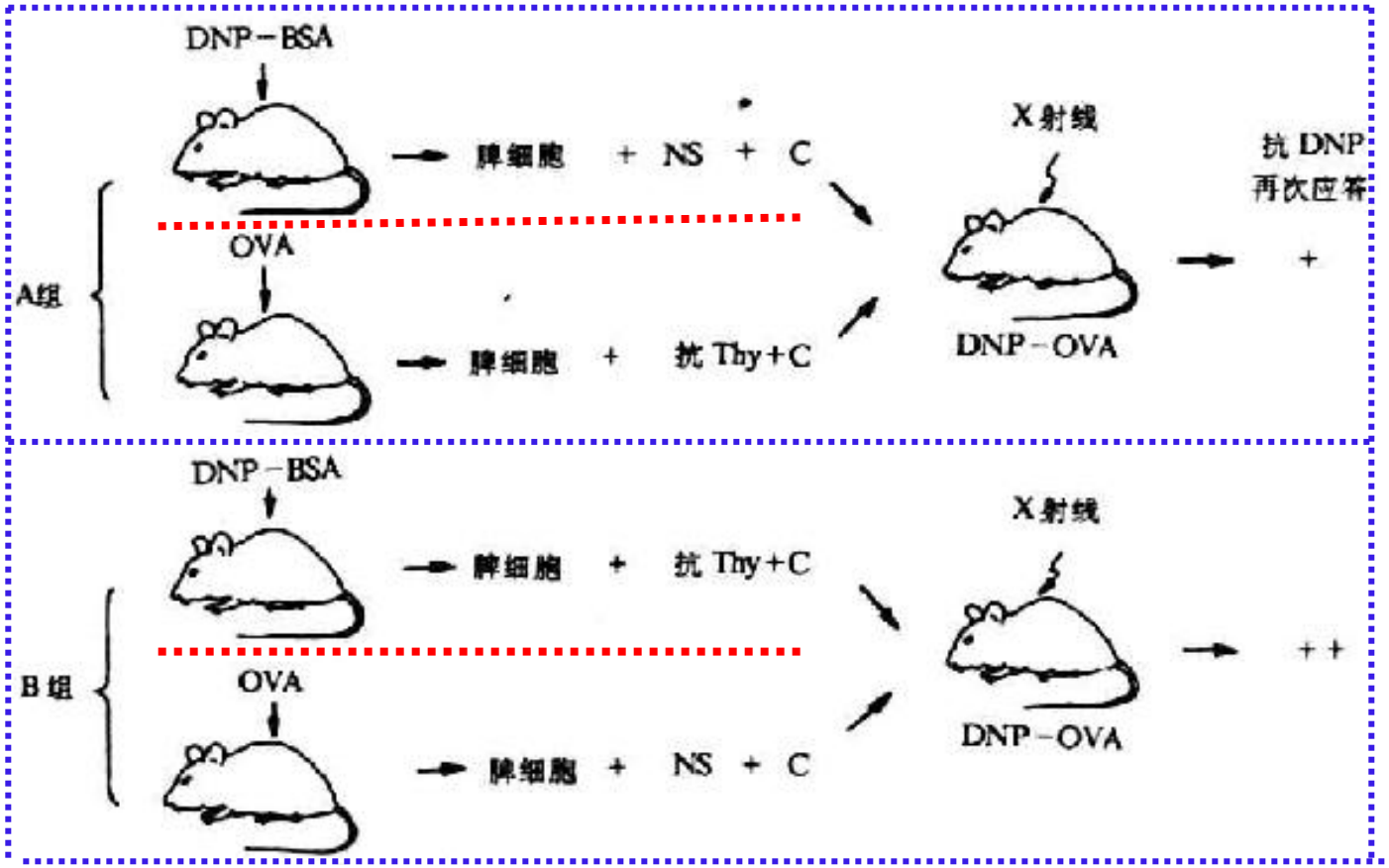
Mitchison, N. A. in *Antibodies* (ed. Frisch, L.) 431–439 (Cold Spring Harbor Laboratory, Cold Spring Harbor, 1967).

Mitchison, NA . T-cell–B-cell cooperation. Nature reviews immunol,2004, APRIL, VOLUME 4, 308-312

Raff experimentation(London,1970):

T cell is the carrier-reactive cell

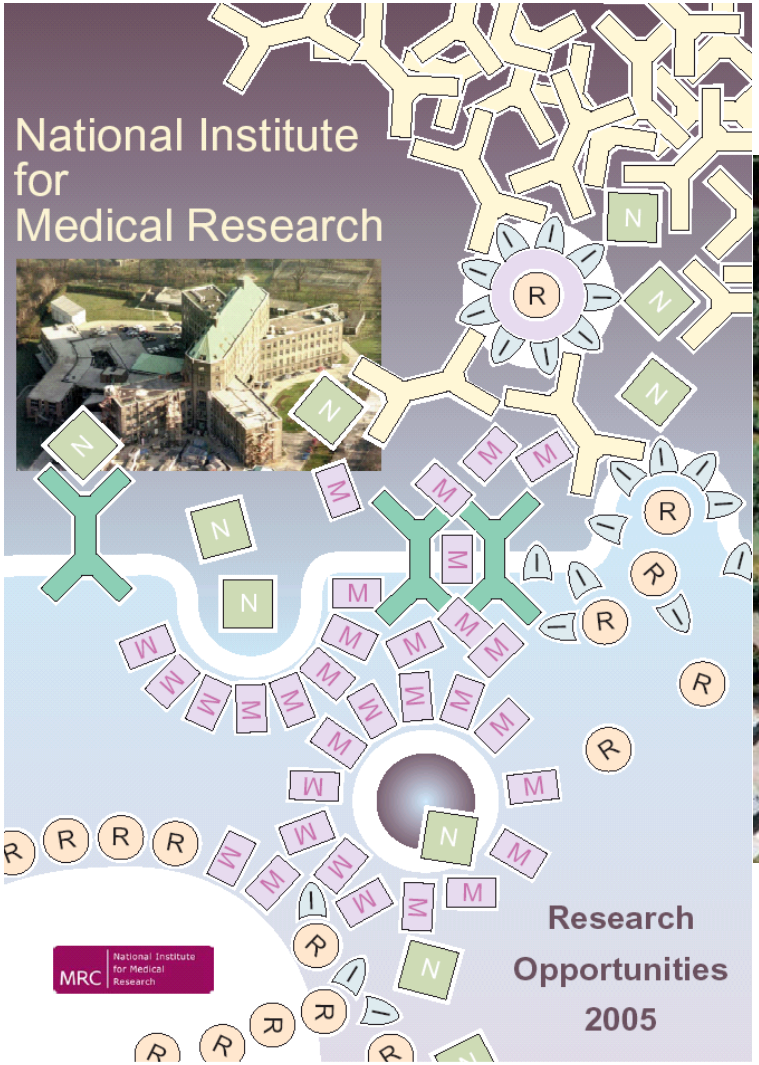
B cell is the hapten-reactive cell



Raff, M. C. Role of thymus-derived lymphocytes in the secondary humoral immune response in mice. *Nature*,226, 1257–1258 (1970).

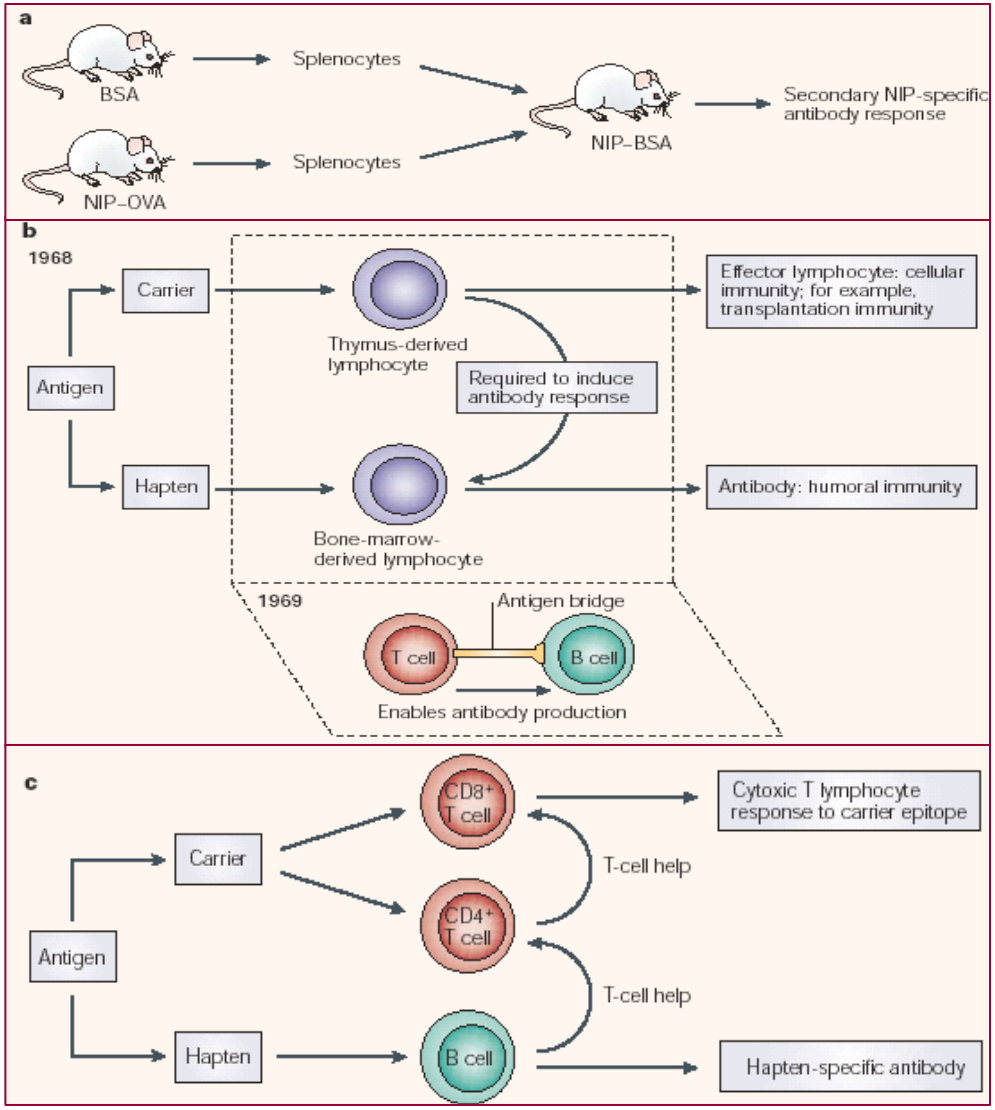
Nature Reviews Immunology **4**; 308-312 (2004); doi:10.1038/nri1334

T-CELL–B-CELL COOPERATION **by** ***N. A. Mitchison***



Nature Reviews Immunology **4**; 308-312 (2004)

T–B cooperation as understood in 1968

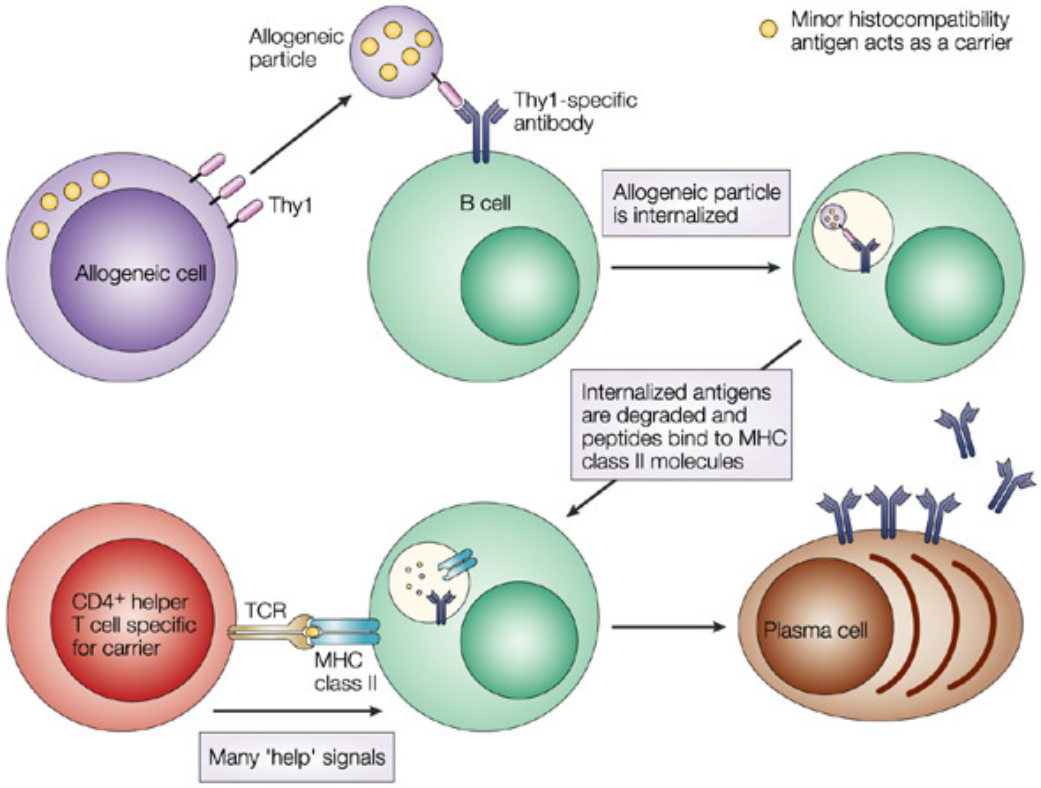


Thymus-derived lymphocytes of the type that mediate transplantation immunity help bone-marrow-derived lymphocytes to produce antibody, by a-then-unknown mechanism. By 1969, the hapten and carrier were thought to form an antigen bridge between T and B cells recognizing the specific components of the antigen, as shown in the inset and adapted from Ref. 36. The bridge helps transmit the signal that activates the B cell to produce antibody.

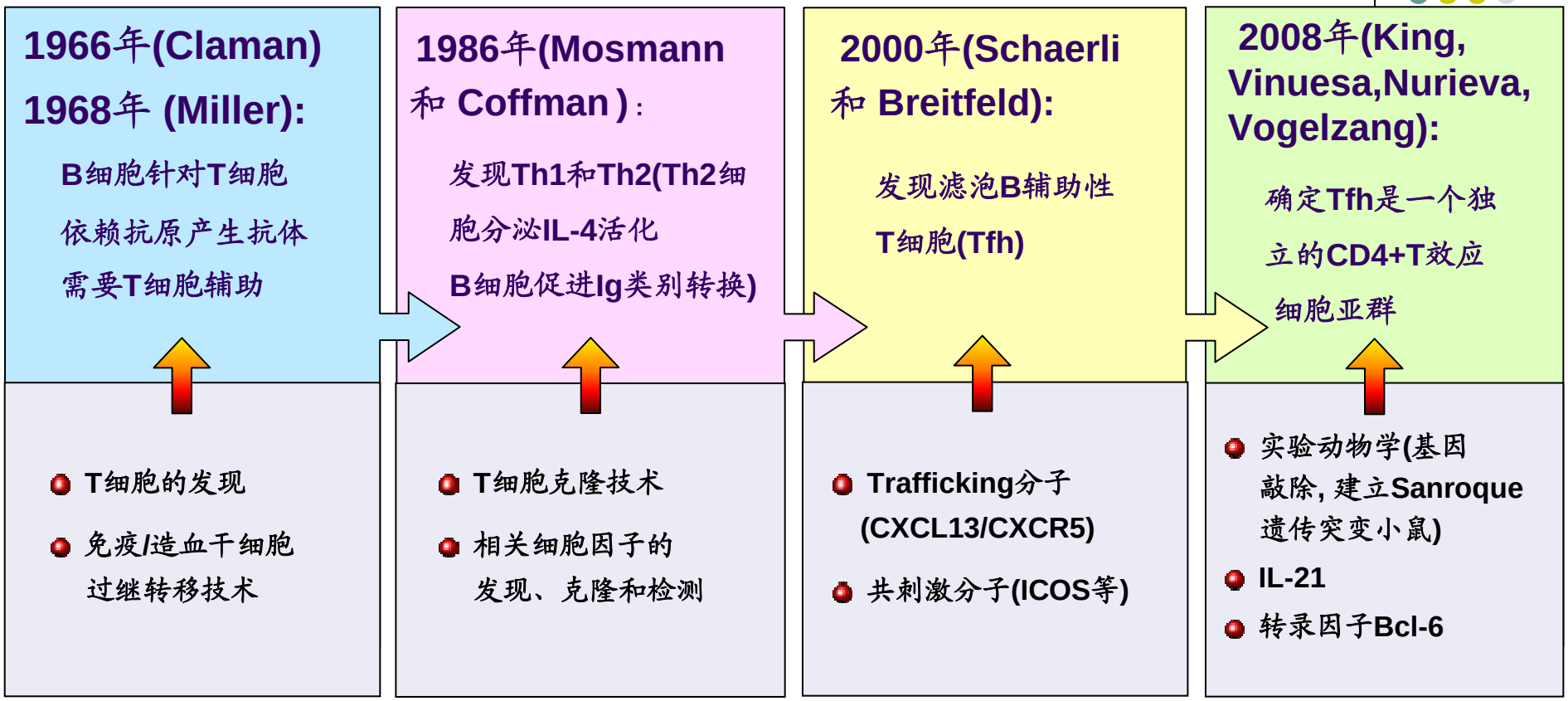
The ideas put forward in 1968 have largely stood the test of time. Antigenic stimulation induces CD4+ T helper (TH) cells that provide help to B cells recognizing an antigen linked to the peptide that activates the CD4+ TH cells. In addition, CD4+ TH cells provide help to the cellular immune response that is elicited by cytotoxic T lymphocytes recognizing other peptides from the same antigen.

Nature Reviews Immunology **4**; 308-312 (2004)

T–B cooperation in the response to allogeneic cells, as adapted from our knowledge in 1992.



Antigenic particles derived from allogeneic cells can be internalized by B cells expressing antigen-specific cell-surface antibodies. The internalized complex is degraded in the endosomal pathway and peptides generated during this process are loaded onto MHC class II molecules and presented at the cell surface. These peptide–MHC-class-II complexes are recognized by CD4+ helper T cells expressing a cognate T-cell receptor (TCR), and the resulting interface between the B and T cell is known as the immunological synapse. The multiple molecular interactions at this site lead to B-cell activation and production of antigen-specific antibodies.



T细胞辅助B细胞——40年研究历史

Cecile King. Nat Rew Immunol,2009;9(11):757

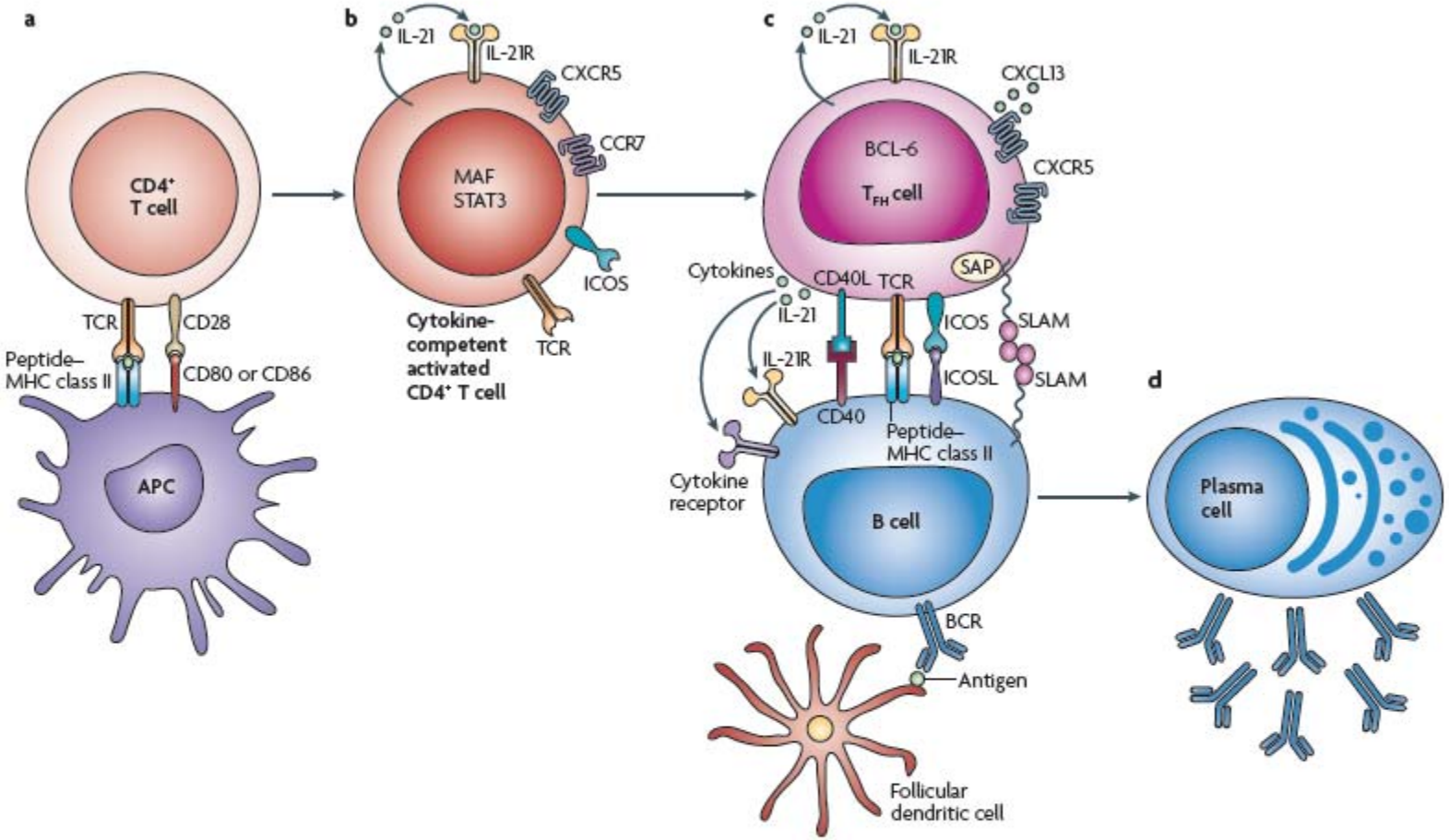
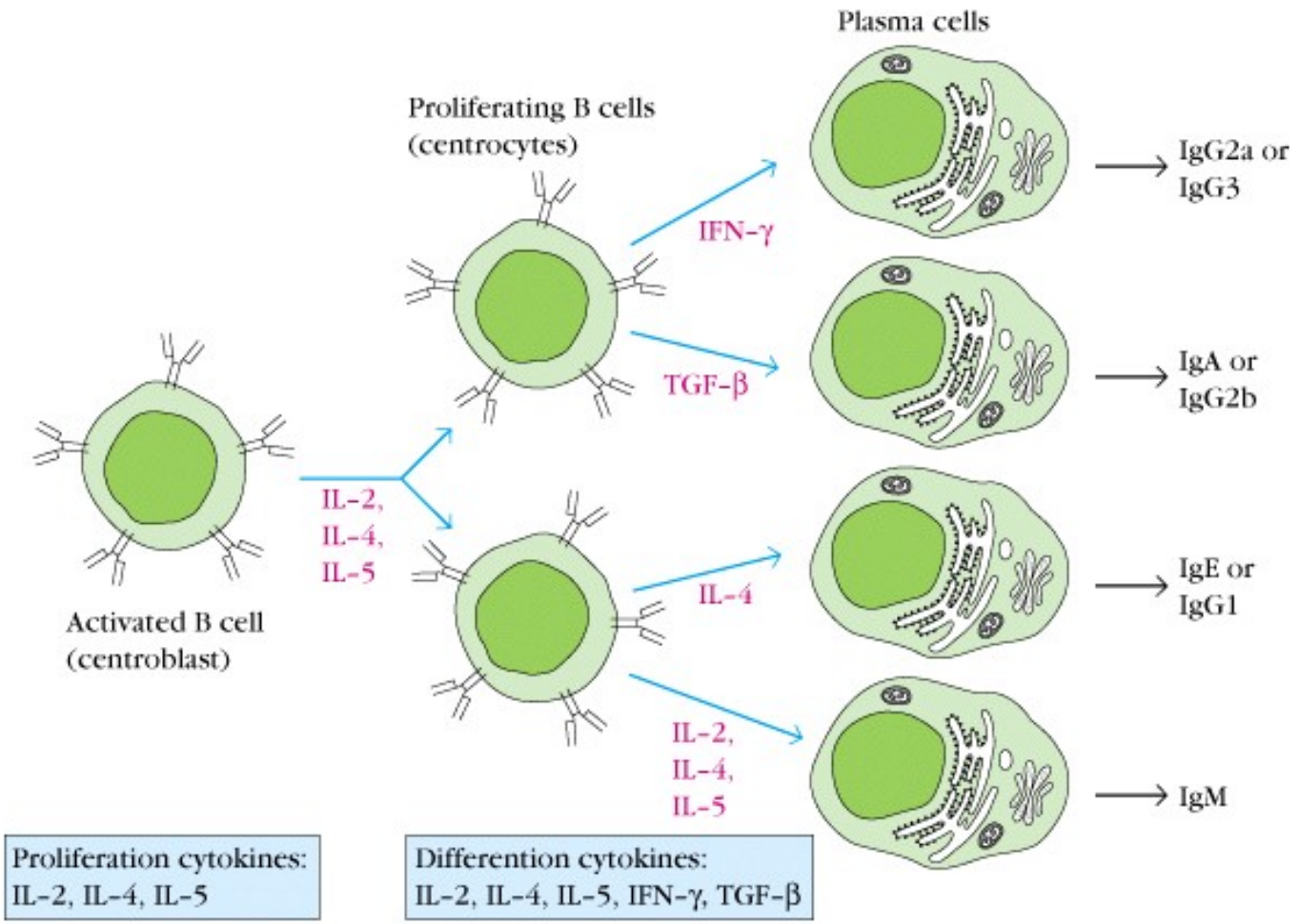


Figure 3 | **The multi-signal pathway for T follicular helper (T_{FH}) cell generation. a** | In the T cell zone of lymphoid tissues, mature dendritic cells expressing CD80 and CD86 present peptide–MHC class II complexes to the T cell receptor (TCR) of naive CD4+ T cells, which constitutively express CD28. **b** | Activated CD4+ T cells produce interleukin-21 (IL-21) and express inducible T cell co-stimulator (ICOS), MAF and signal transducer and activator of transcription 3 (STAT3) and begin their acquisition of cytokine competency (for example, IL-4 or interferon-γ (IFNγ) production) in the T cell zone. **c** | Sustained signalling of activated CD4+ T cells through the TCR, ICOS and IL-21 receptor (IL-21R) at the T cell–B cell border leads to the modulation of cell surface molecules that are important for migration and T cell–B cell interactions, such as increased CXC-chemokine receptor 5 (CXCR5) expression and decreased CC-chemokine receptor 7 (CCR7) expression, and expression of ICOS, CD40 ligand (CD40L), OX40 and signalling lymphocytic activation molecule (SLAM) family members. Follicular dendritic cells bearing antigen interact with maturing B cells in the germinal centre reaction. **d** | Migration of functional T_{FH} cells to B cell follicles and delivery of T cell help to B cells support the selection of activated antibody-secreting plasma cells in germinal centres. APC, antigen-presenting cell; BCL-6, B cell lymphoma 6; BCR, B cell receptor; CXCL13, CXC-chemokine ligand 13; ICOSL, ICOS ligand; SAP, SLAM-associated protein.

9.Cytokine induction of B-cell proliferation and class switching



Cecile King. New insights into the differentiation and function of T follicular helper cells. Nat Rew Immunol,2009;9(11):757

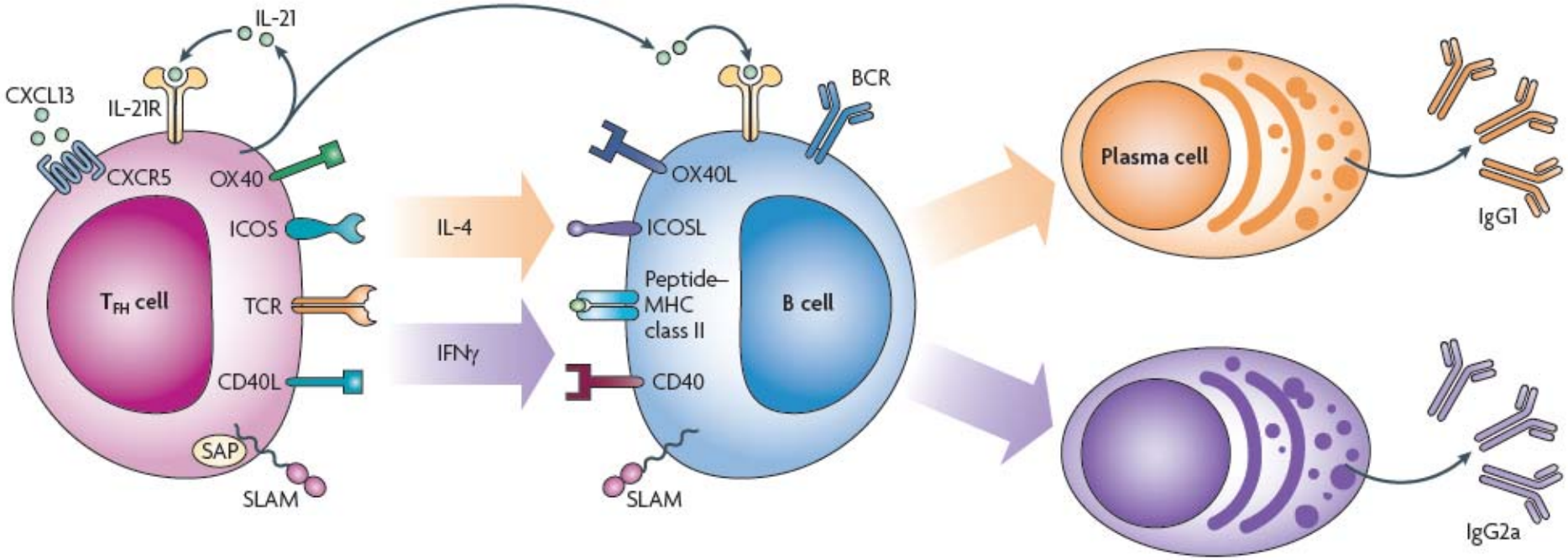
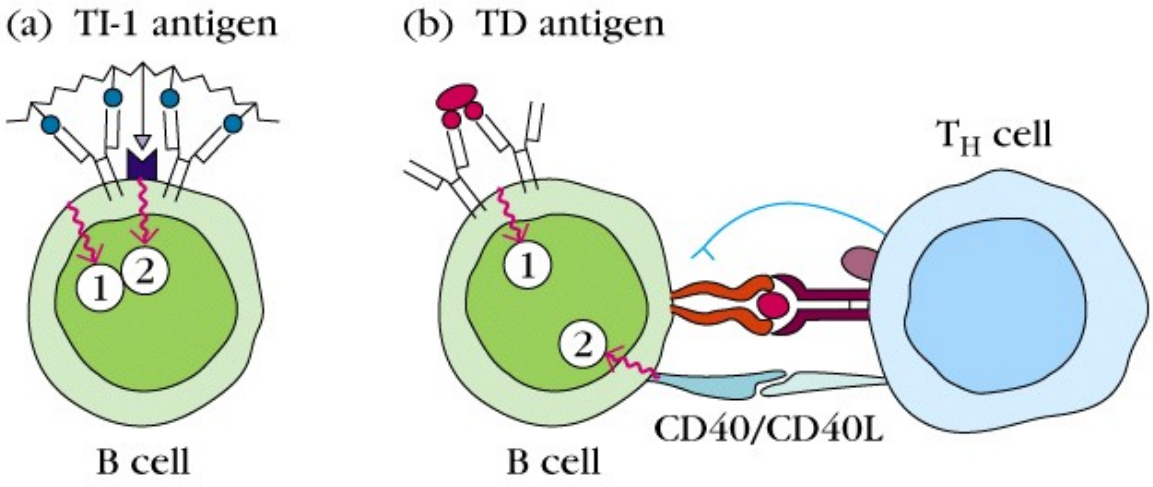
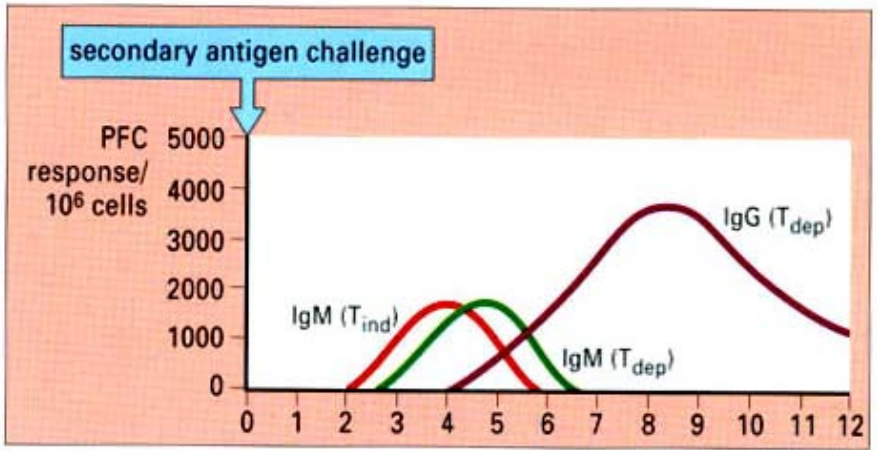


Figure 2 | **Antibody class switching is directed by cytokines.** A range of cytokines produced by T follicular helper (T_{FH}) cells can direct antibody class switching. The acquisition of T cell cytokine competency begins in the T cell zone and precursor T_{FH} cells have the capacity to induce class switching during their interaction with B cells at the border of the T cell zone and B cell follicle. Interleukin-4 (IL-4) induces the switch to IgG1 production (and then IgE production, not shown), and interferon-γ (IFNγ) induces the switch to IgG2a production. BCR, B cell receptor; CXCL13, CXC-chemokine ligand 13; CXCR5, CXC-chemokine receptor 5; ICOS, inducible T cell co-stimulator; IL-21R, IL-21 receptor; L, ligand; SAP, SLAM-associated protein; SLAM, signalling lymphocytic activation molecule; TCR, T cell receptor.

10.Competency Signals in TI and TD Antigen Activation





Comparison of secondary immune responses to T_{dep} and T_{ind} antigens *in vitro*

The End