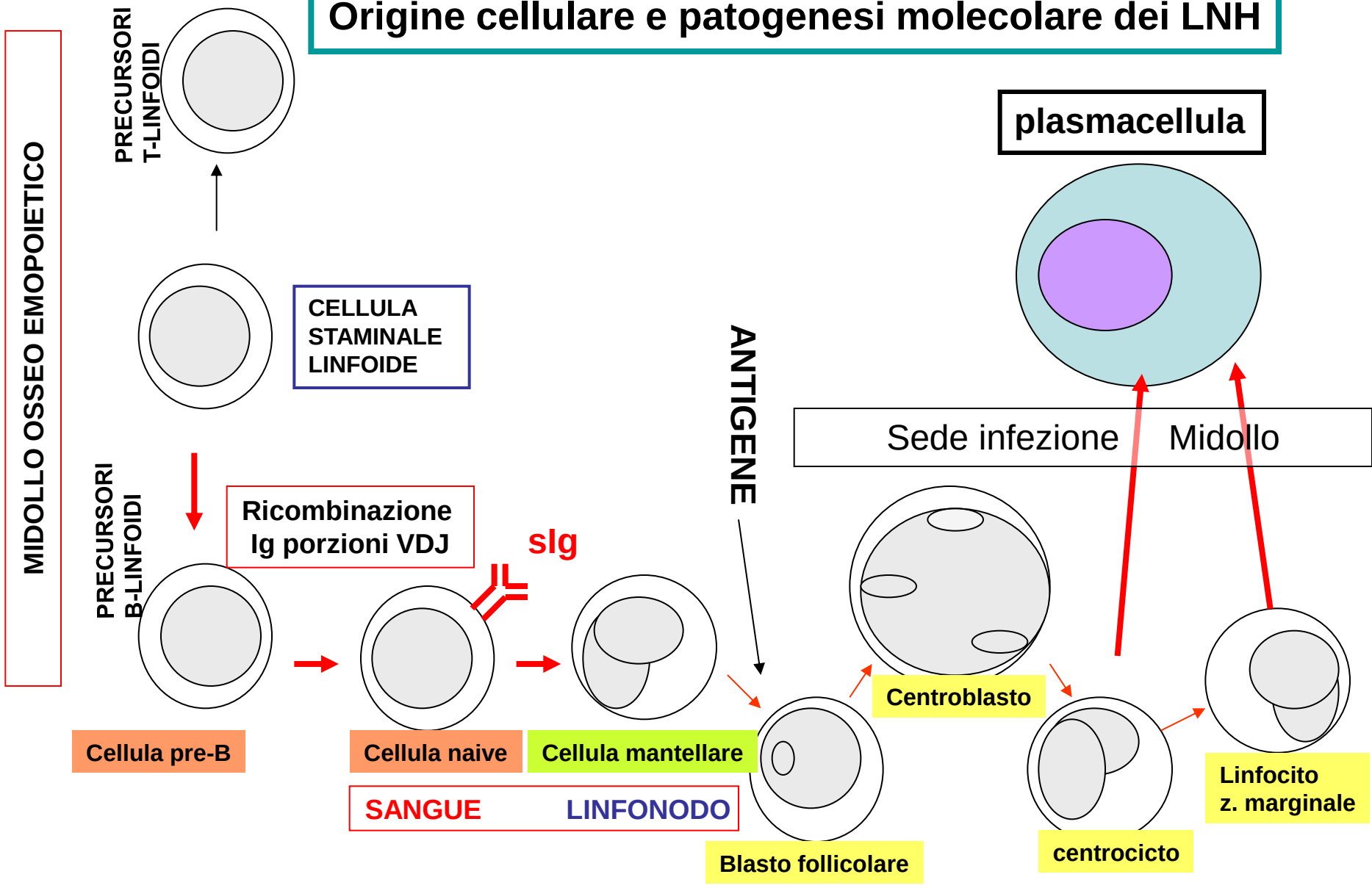
Definizione Linfomi

- Espansione clonale di una cellula linfoide bloccata ad un determinato stadio di maturazione

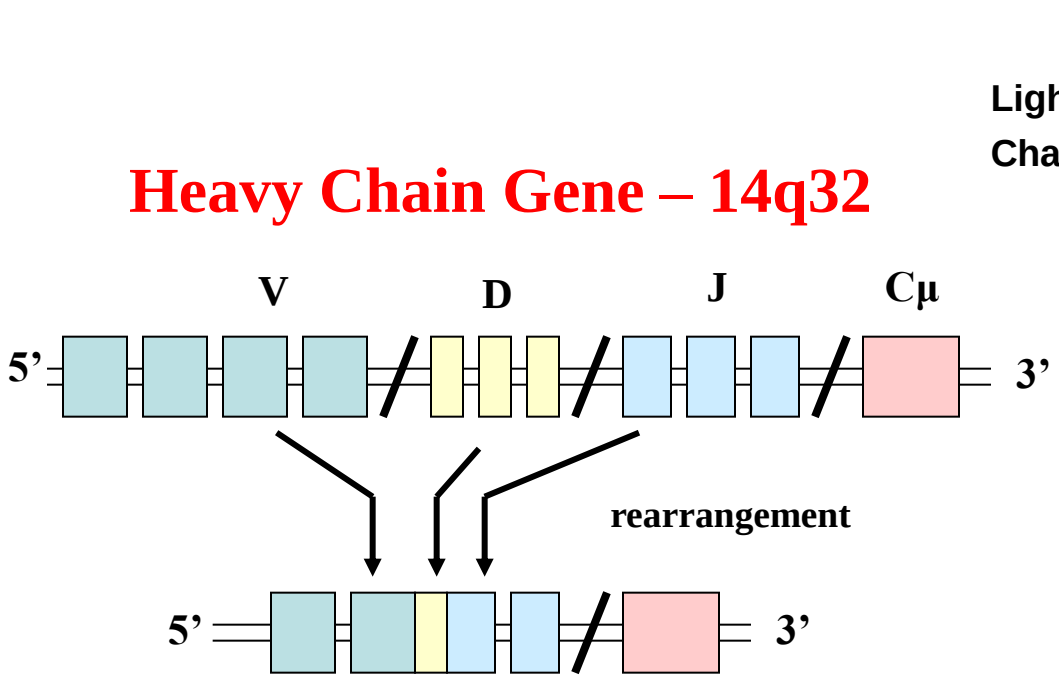
- Localizzazione linfonodale, emato-midollari, extra-linfonodale

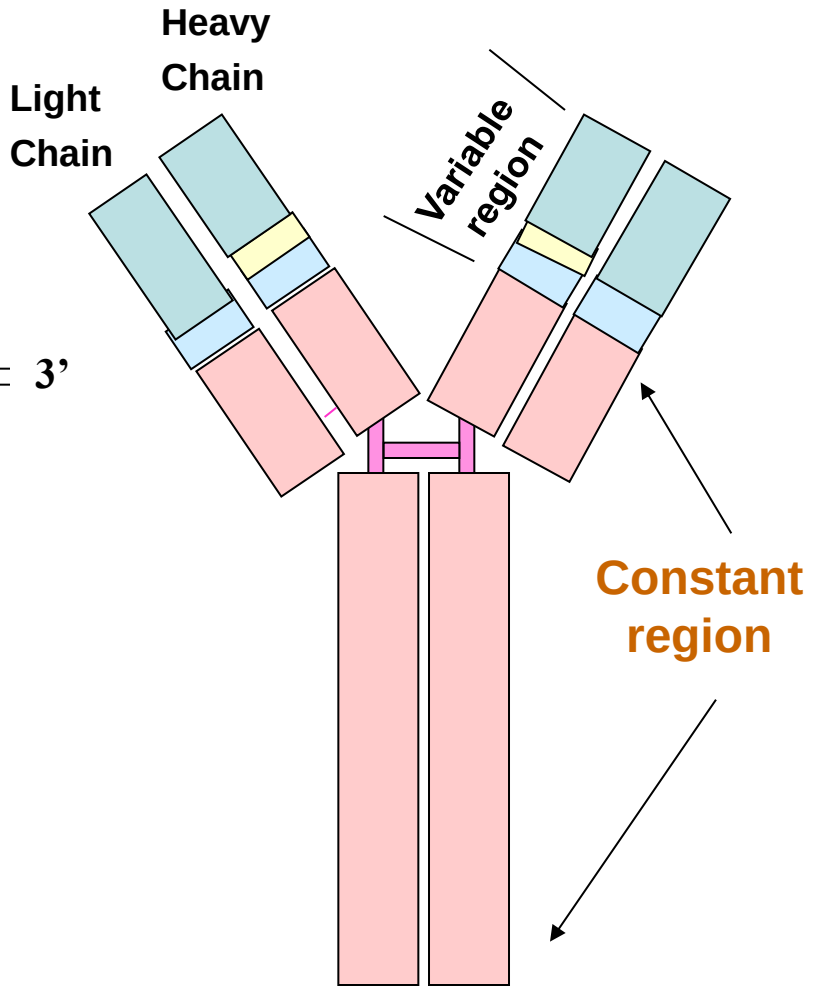
Origine cellulare e patogenesi molecolare dei LNH

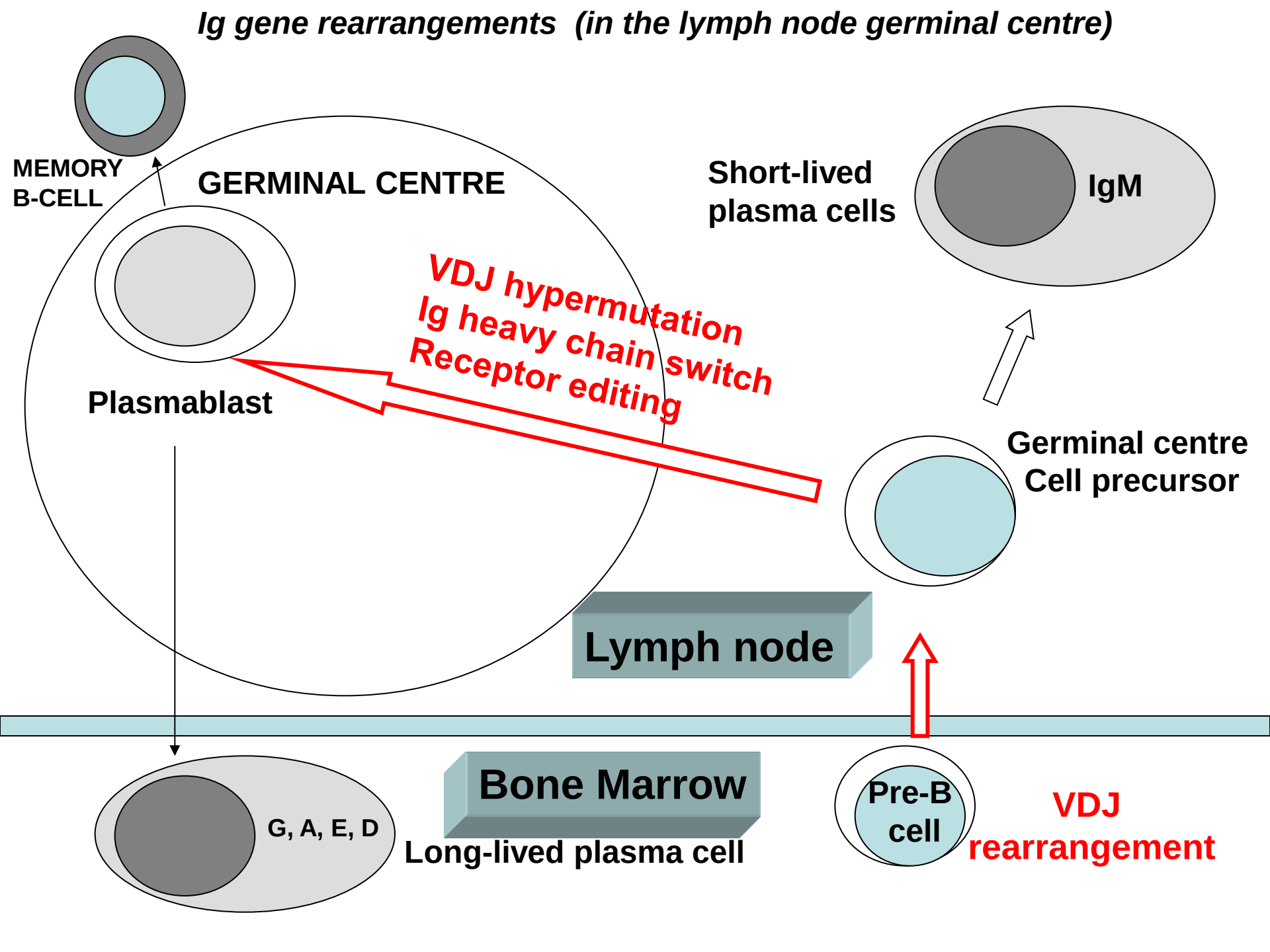


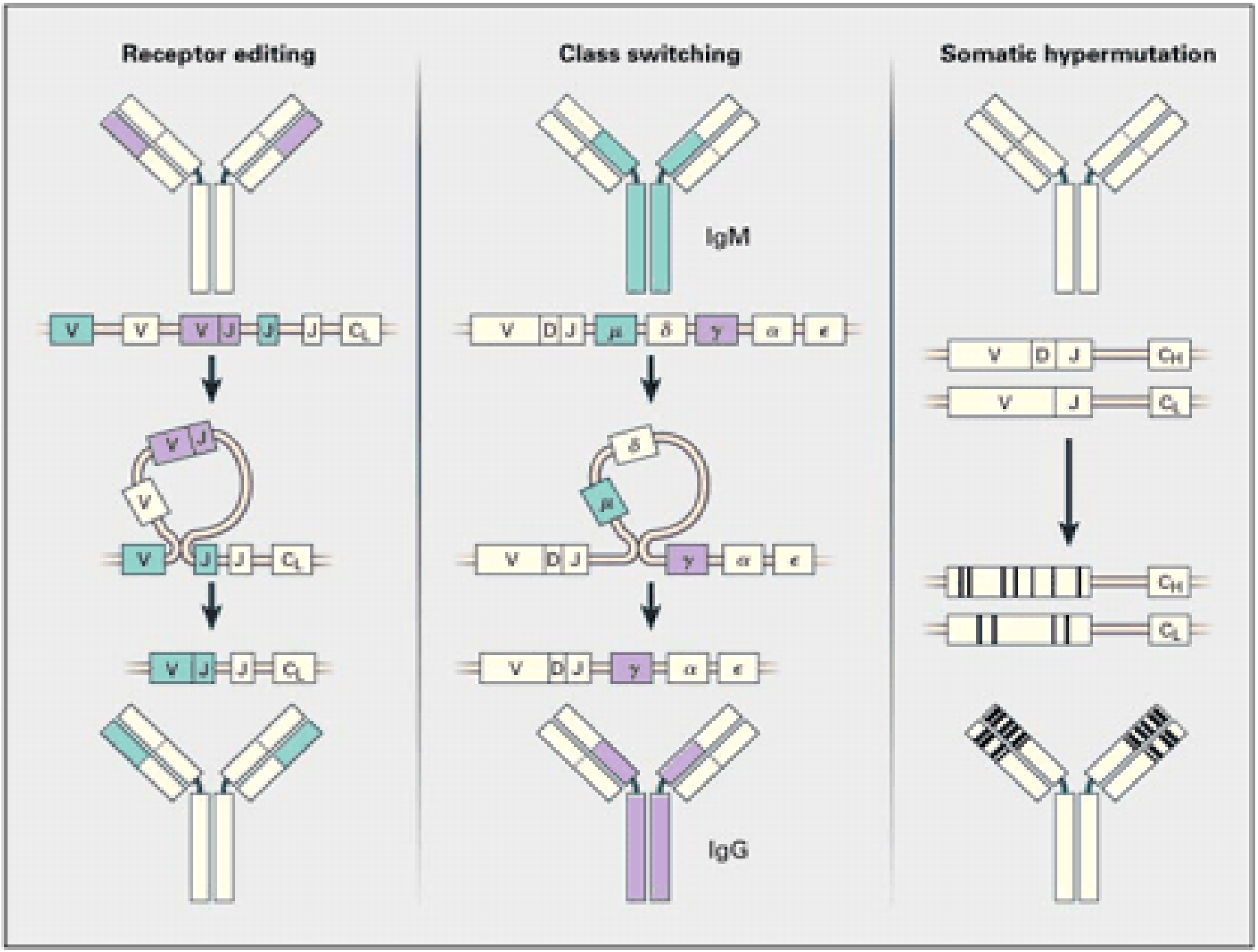
Schema della differenziazione B-linfocitaria

Ig heavy chain nrearrangement (occurs in the bone marrow)

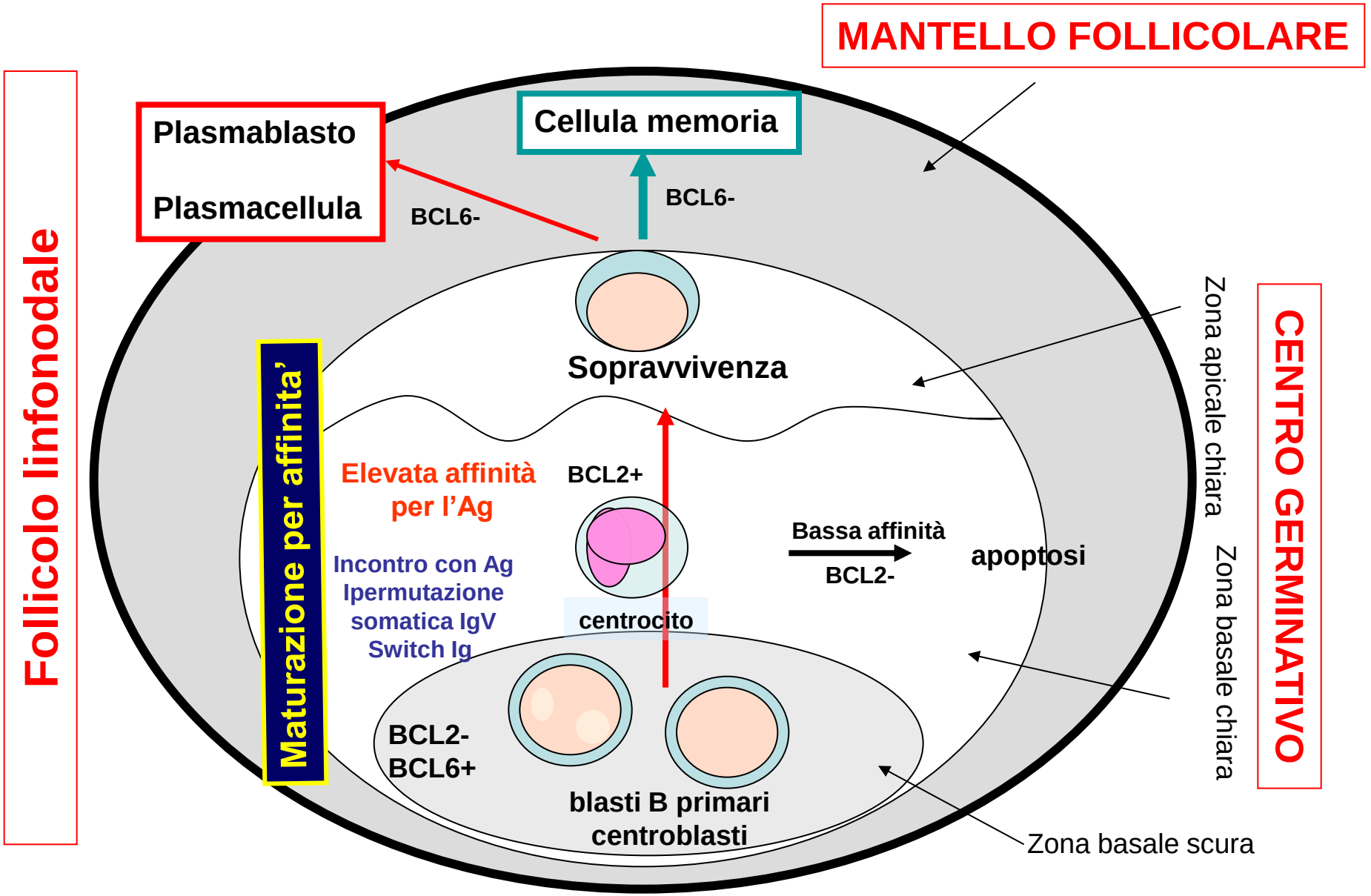





Ig gene rearrangements (in the lymph node germinal centre)
MEMORY B-CELL
GERMINAL CENTRE
Short-lived plasma cells
IgM
VDJ hypermutation
Ig heavy chain switch
Receptor editing
Plasmablast
Germinal centre Cell precursor
Lymph node
Bone Marrow
G, A, E, D
Long-lived plasma cell
Pre-B cell
VDJ rearrangement

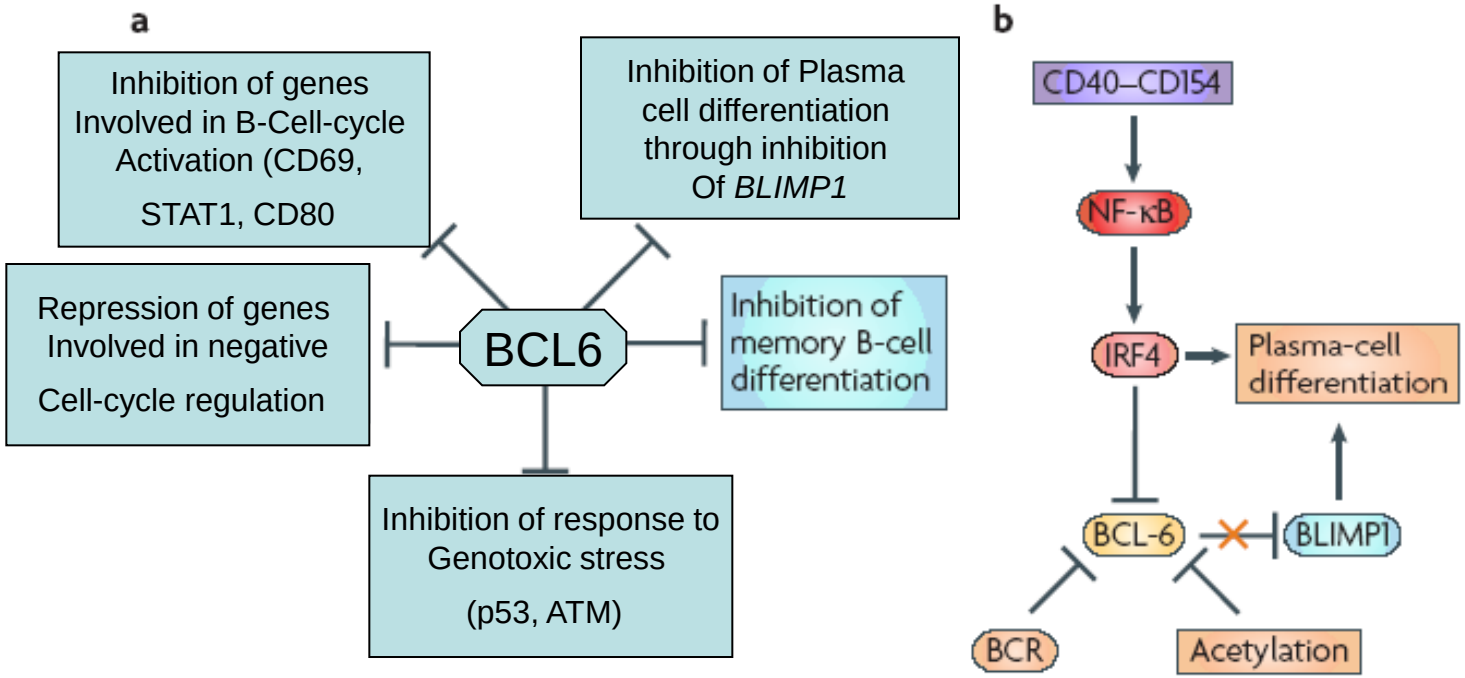

Receptor editing
Class switching
Somatic hypermutation
IgM
IgG
V
D
J
μ
δ
γ
α
ε
CH
CL

Formazione del centro germinativo



a) BCL6 è importante perché permette la formazione del centro germinativo
- Permette la proliferazione massiva dei centroblasti
- permette la divisione in cellule che sviluppano mutazioni genetiche (SHM) inibendo p53 e ATM
- blocca la attivazione e la differenziazione

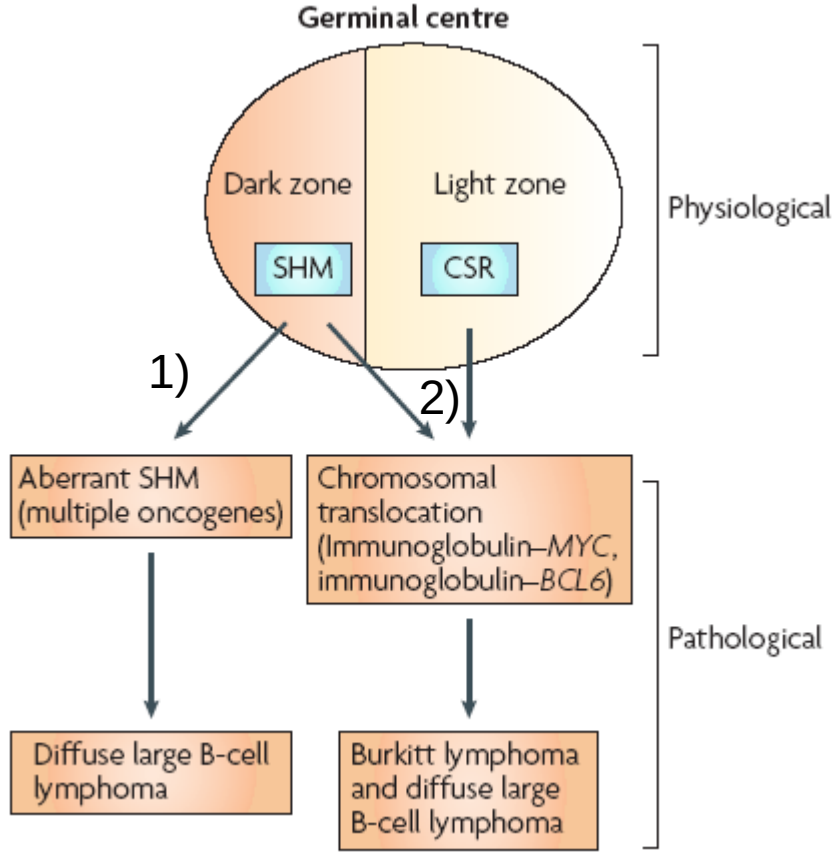
-b) la stimolazione del B Cell Receptor (BCR) da parte dell'Ag e le interazioni e l'attivazione del signalling indotto da CD40 e derivante dall'interazione con i linfociti CD4 porta alla repressione di BCL6



Modificato da
Klein U, Dalla Favera R
Nature Immunol, 2008

Due meccanismi genetici principali sono alla base della B-linfomagenesi

1) Ipermutazione somatica coinvolgente geni chiave nella maturazione e differenziazione linfocitaria
2) Traslocazioni coinvolgenti il gene Ig e altri partners

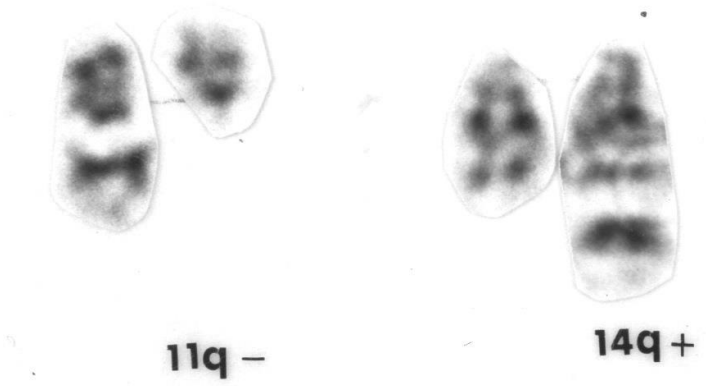


Esempi:
1) Mutazioni delle sequenze regolatrici di BCL6 coinvolte nella attivazione di un circuito di auto-repressione trascrizionale

2) Mutazioni sequenze promotrici BCL2 e conseguente insensibilità di BCL2 verso l'azione inibitrice svolta da BCL6 via Miz1

Modificato da
Klein U, Dalla Favera R
Nature Immunol, 2008

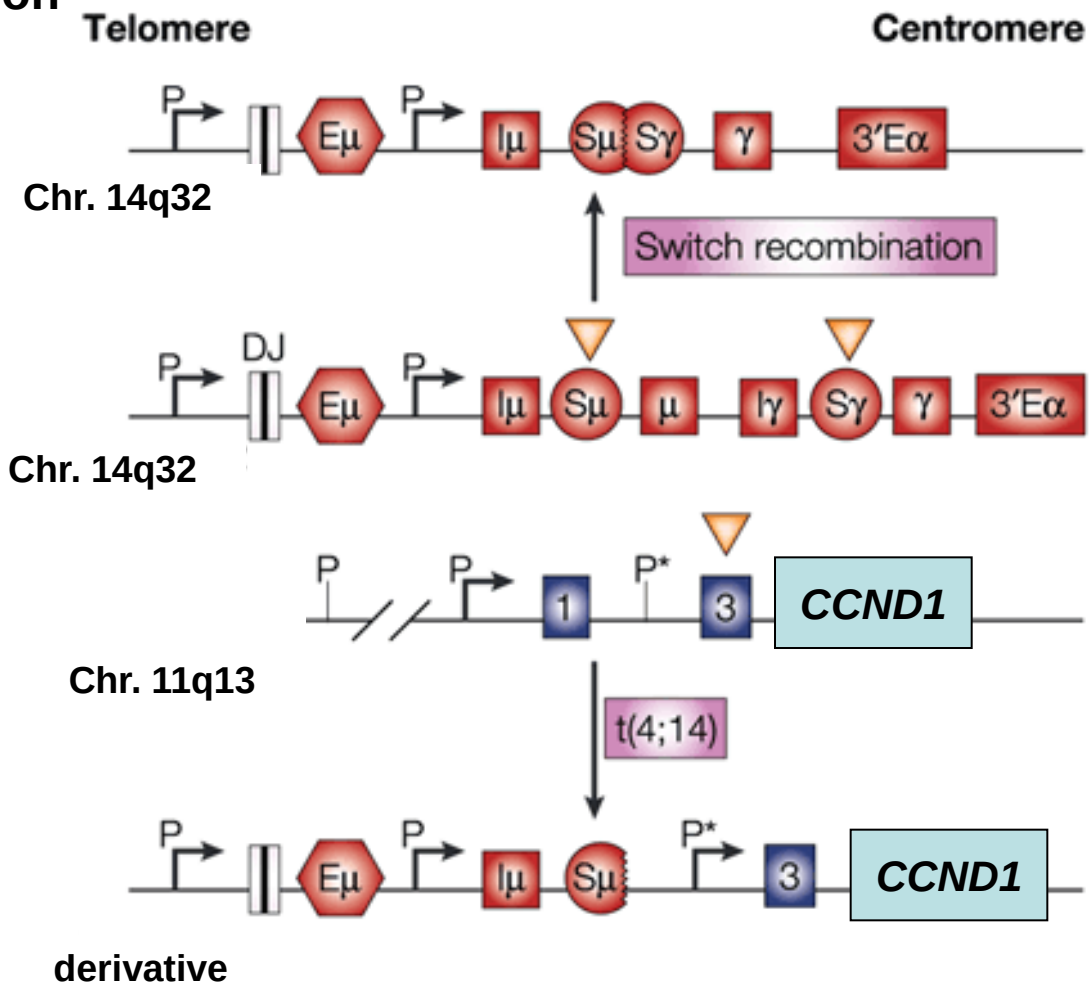
LYMPHOMAGENESIS
Translocation involving the Ig gene at 14q42



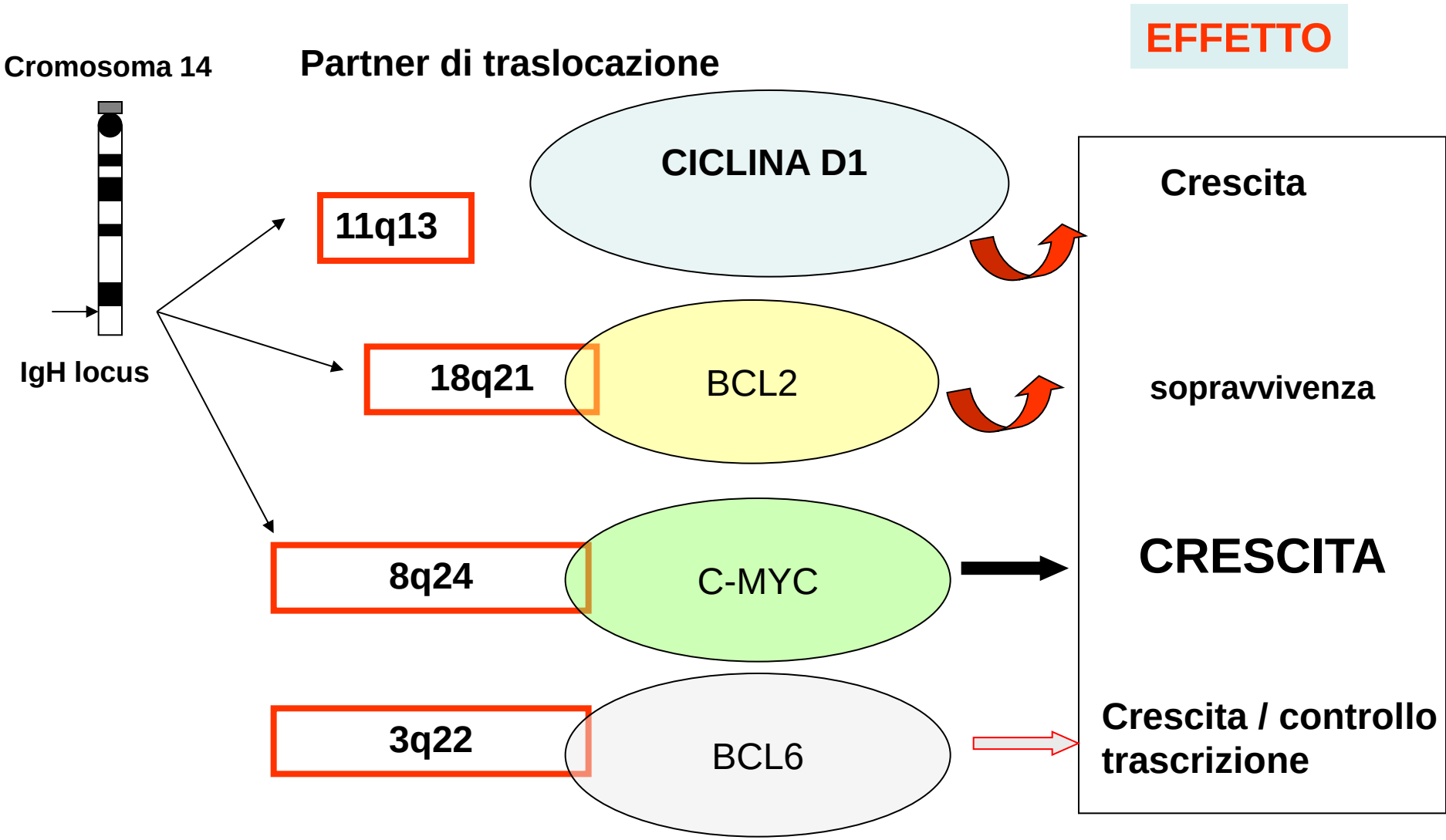
Errors in IgH recombination lead to translocation

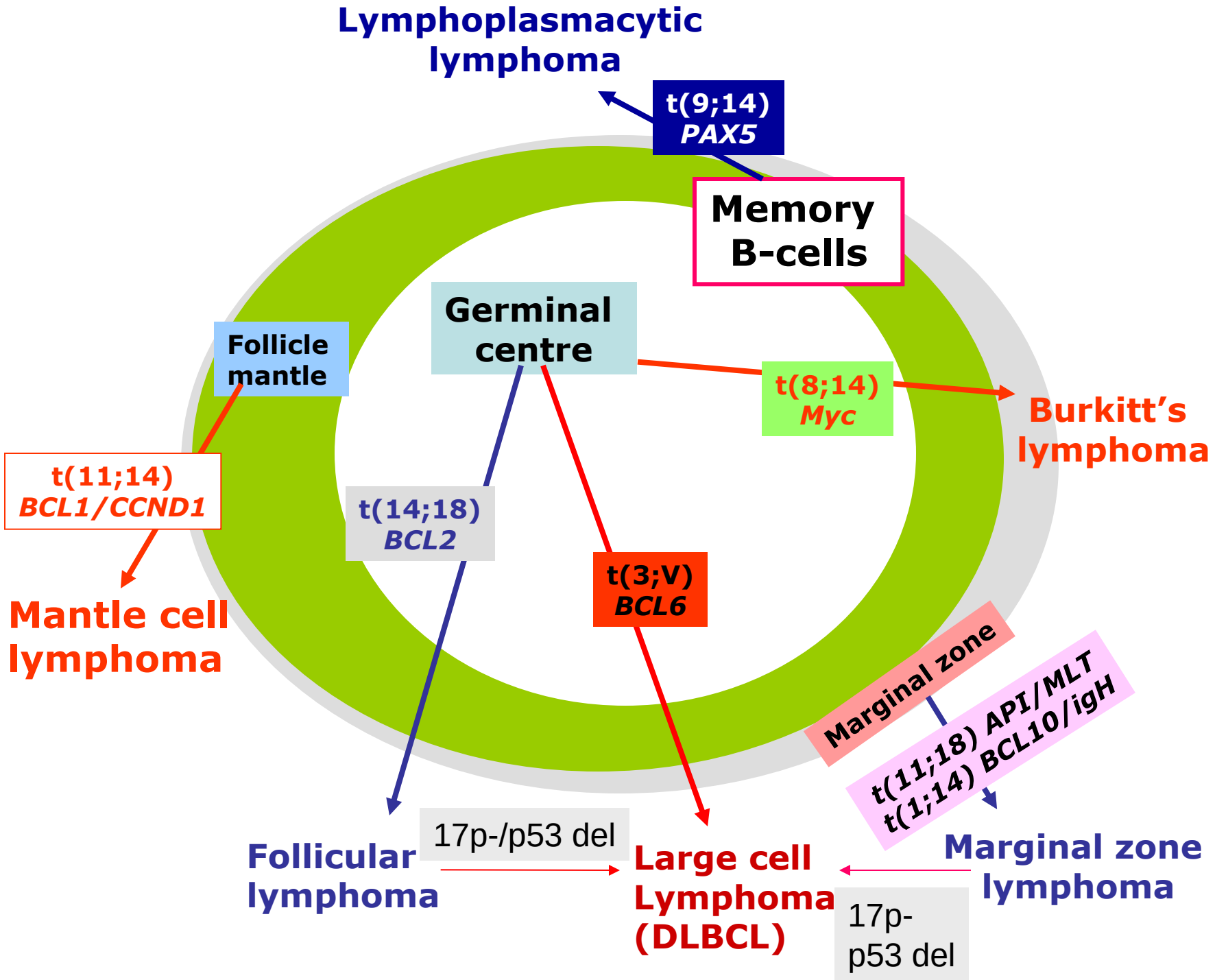
Normal IgH recombination

t(11;14)(q13;q32) juxtaposes IgH and CCND1



ALCUNE TRASLOCAZIONI PRIMARIE IMPORTANTI NELLA PATOGENESI DEI LINFOMI




Lymphoplasmacytic lymphoma
t(9;14) PAX5
Memory B-cells
Germinal centre
Follicle mantle
t(8;14) Myc
Burkitt's lymphoma
t(11;14) BCL1/CCND1
t(14;18) BCL2
t(3;V) BCL6
Mantle cell lymphoma
Marginal zone
t(11;18) API/MLT
t(1;14) BCL10/igH
Marginal zone lymphoma
17p-/p53 del
Follicular lymphoma
Large cell Lymphoma (DLBCL)
17p- p53 del

Linfomi MALT

- Eziologia infettiva:

  HP

  C. Jejuni – immunoproliferative small intestinal disease

  B. burgdoferi – MALToma cutaneo

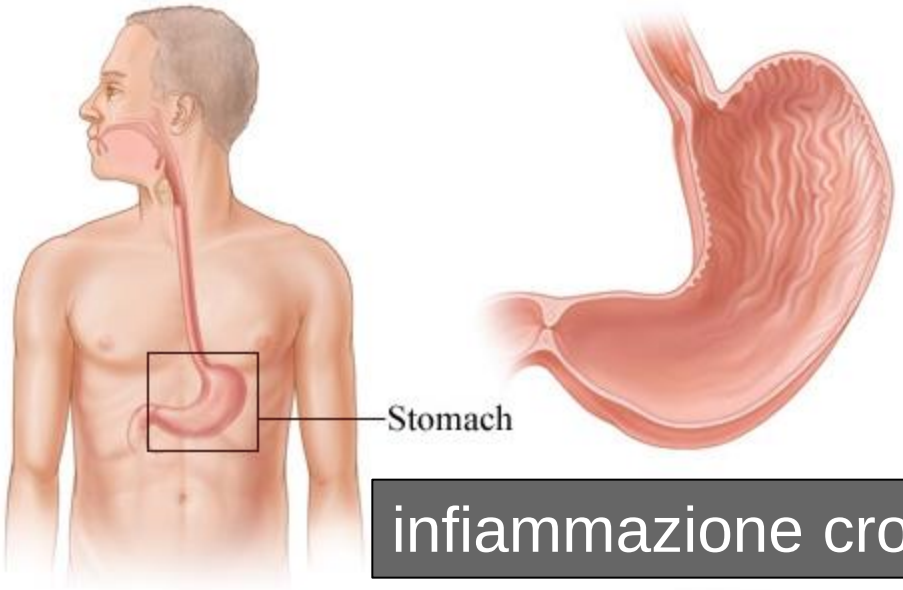
  C. psittaci – linfoma MALT orbitario

  HCV – linfoma della zona marginale splenico

- Eziologia autoimmune:

  Tiroidite di Hashimoto – linfoma marginale tiroideo

  S. Di Sjogren – linfoma marginale delle ghiandole salivari

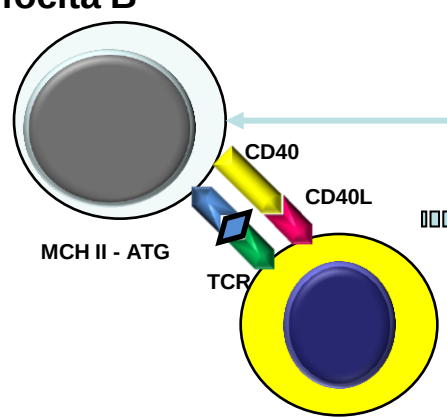


In condizioni fisiologiche lo stomaco NON possiede tessuto linfoide associato alle mucose (MALT)

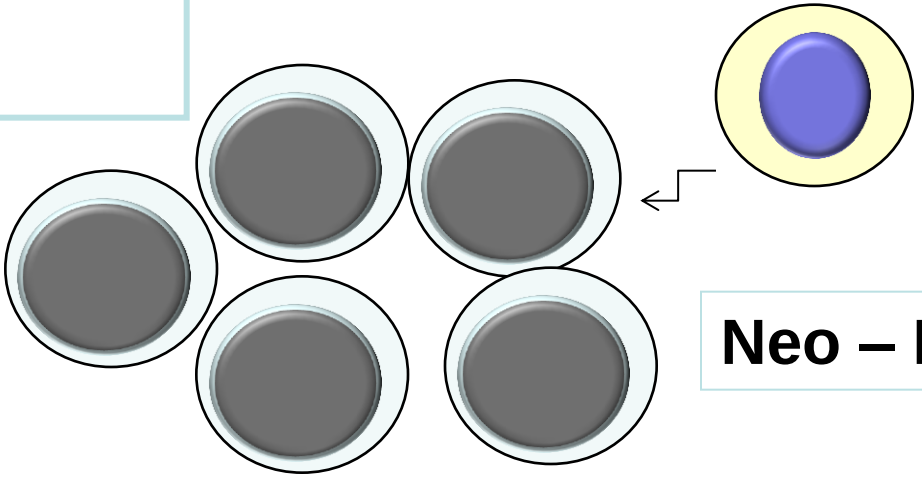
infiammazione cronica da H. pylori

Linfociti CD8: controllo sulla proliferazione B

linfocita B

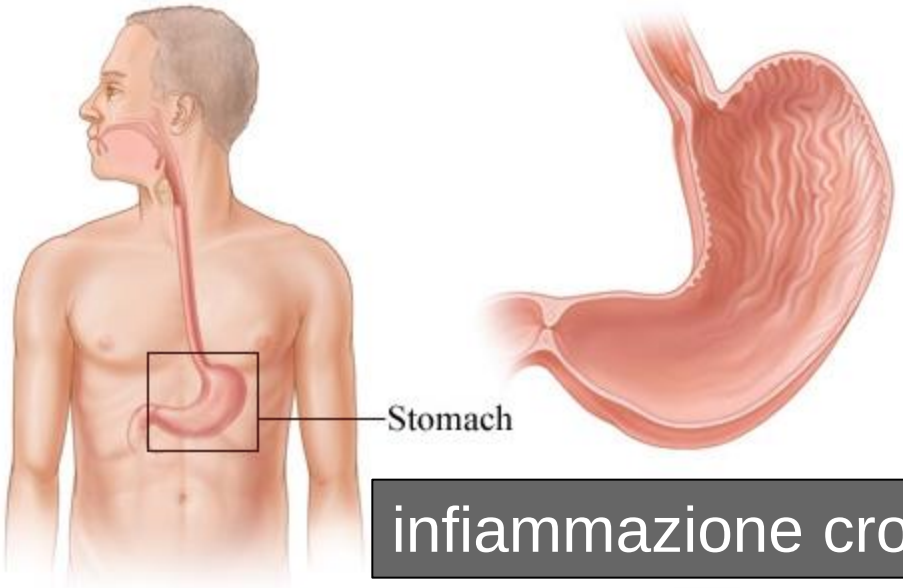


linfocita T_H H. pylori specifico (Ureasi, CagA, VacA, HSP)



Proliferazione ed organizzazione di follicoli linfatici

Neo – MALT

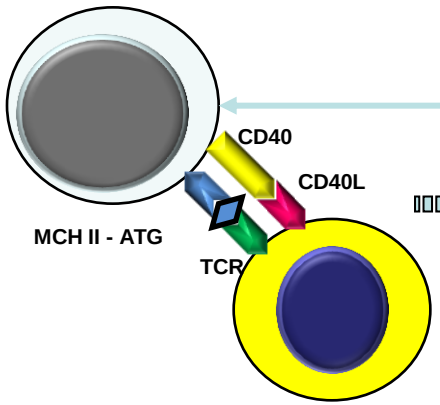


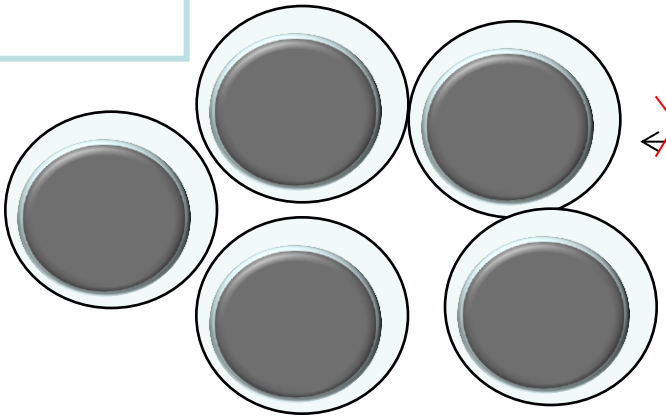
In condizioni fisiologiche lo stomaco NON possiede tessuto linfoide associato alle mucose (MALT)

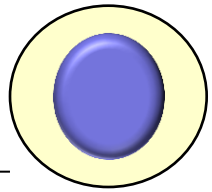
infiammazione cronica da H. pylori

Linfociti CD8
Viene meno
il controllo sulla
proliferazione B

linfocita B







Neo – MALT

Danno
genetico

linfocita T_H H. pylori specifico
(Ureasi, CagA, VacA, HSP)

Proliferazione ed
organizzazione
di follicoli linfatici

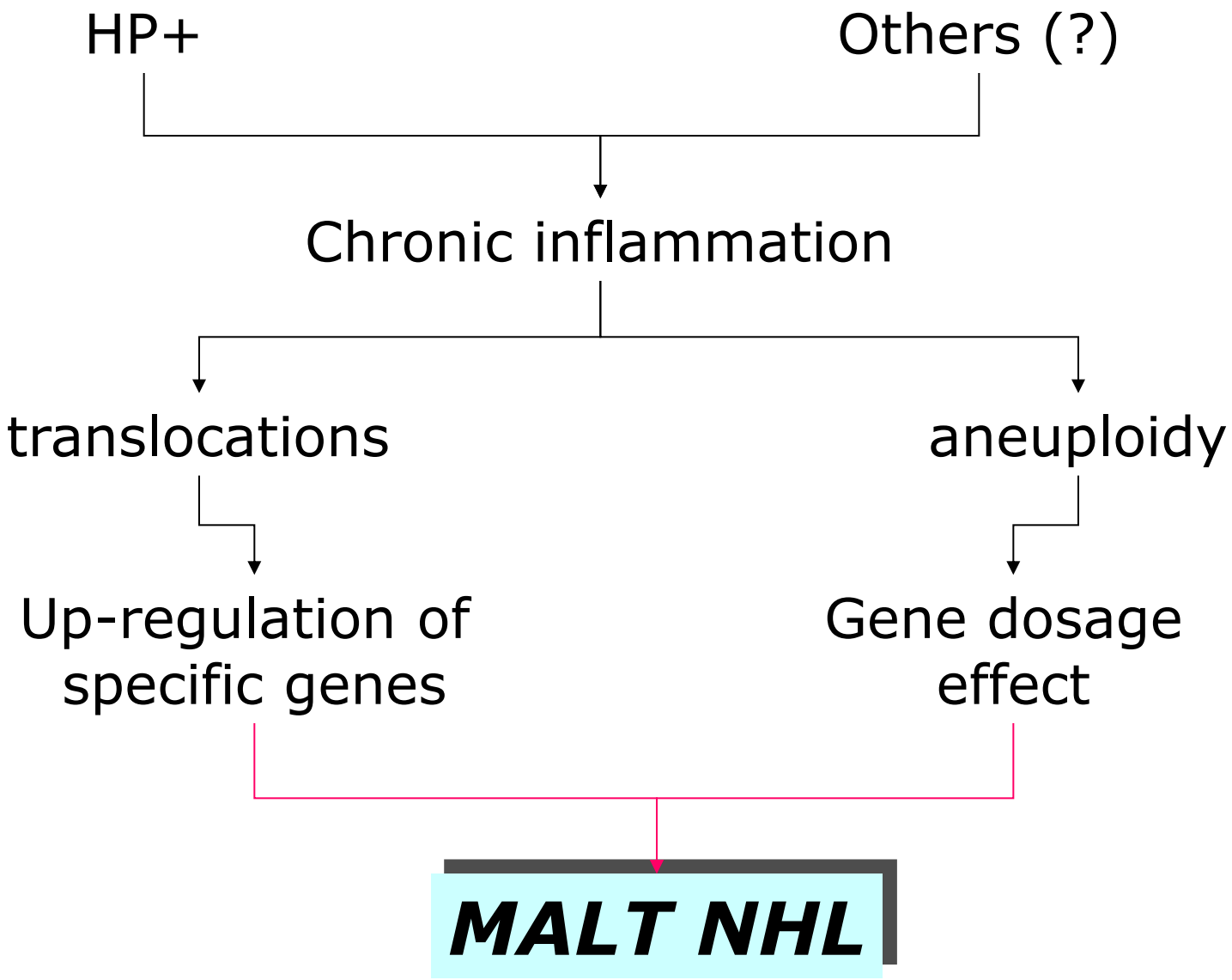
Flogosi
Neutrofili attivati (?)
ROS (?)

Principali alterazioni Citogenetico-molecolari

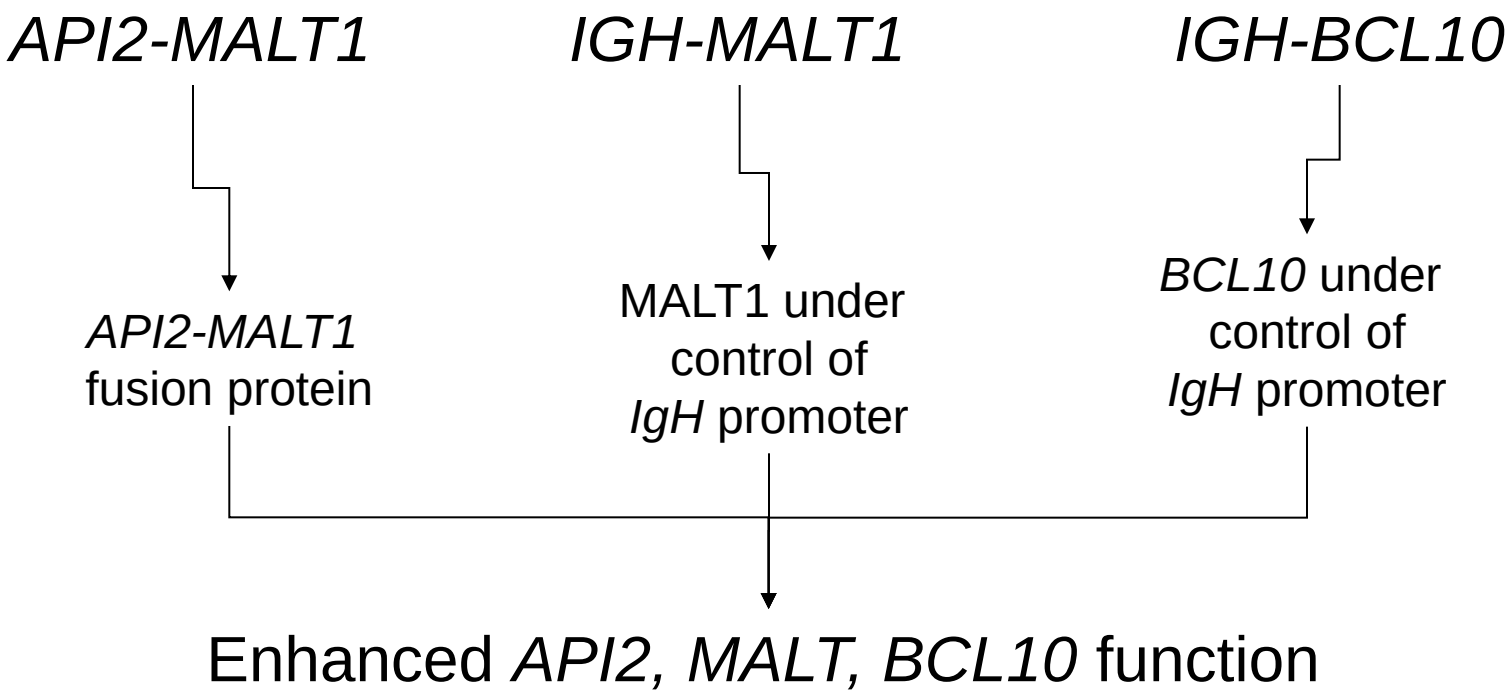
t (11;18)(q21;q21)	API2-MALT1
t (14;18)(q32;q21)	IGH-MALT1
t(1;14)(p22;q32)	IGH-BCL10
t(3;14)(p13;q32)	IGH-FOXP1

Aneuploidie dei cromosomi 3, 7, 12, 18

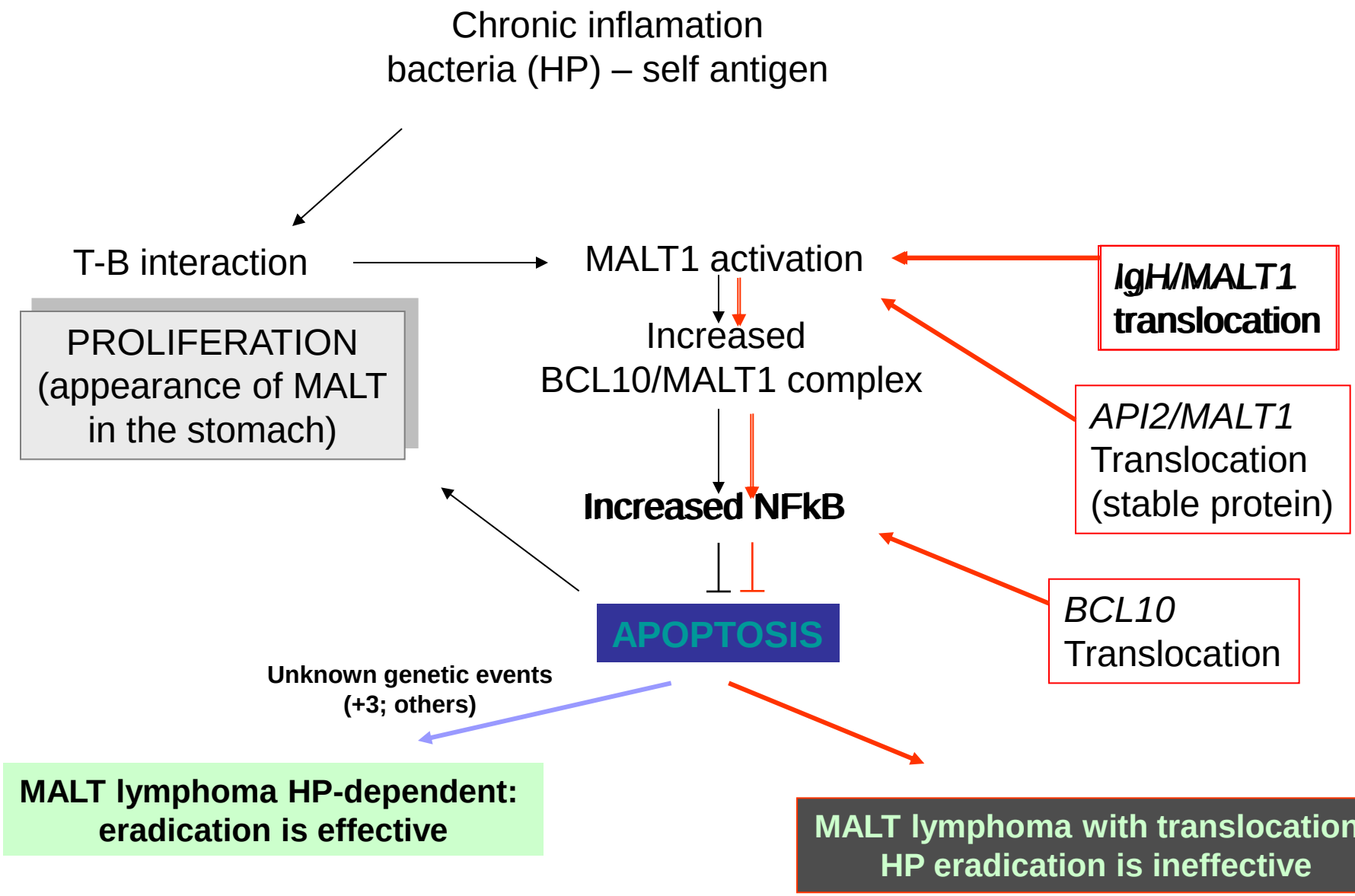
Genetic pathways leading to MALT NHL



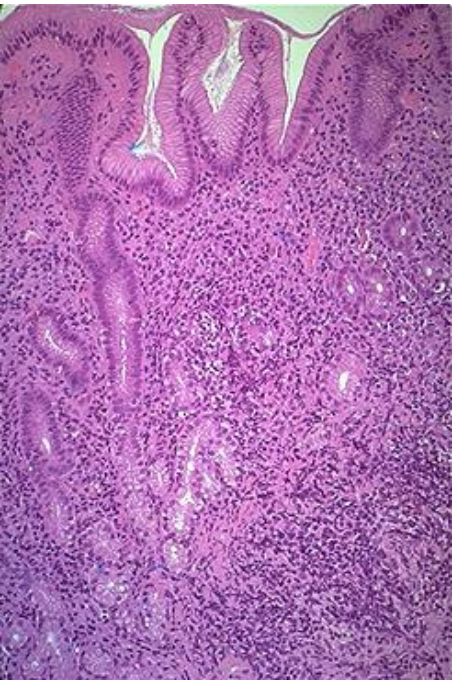
Significance of translocations



Role of chronic inflamation and translocations in the pathogenesis of MALT NHL



Gastric MALT NHL



Low grade gastric MALT NHL is usually caused by HP infection.

It is an indolent disease but may become locally aggressive, spread, or undergo high grade transformation.

Treatment of the infection cures the disease in ~70% of cases.

Resistant or non-localised disease is treated with low dose radiotherapy or single chemotherapy

t(11;18) tumours (25% of total) rarely if ever respond to H pylori treatment, are locally aggressive, but rarely undergo high grade transformation.

Radiotherapy or chemotherapy ± rituximab should be considered early in stage IIE disease and for all t(11;18) tumours.