2019

Progetto Ematologia Romagna

Il bcl2 è il gene della "vita"; le sue alterazioni (mutazione, traslocazioni e amplificazioni) inducono malattie linfo-mieloproliferative

Nicoletta Testoni

BCL-2

Localizzato sul cromosoma 18q21

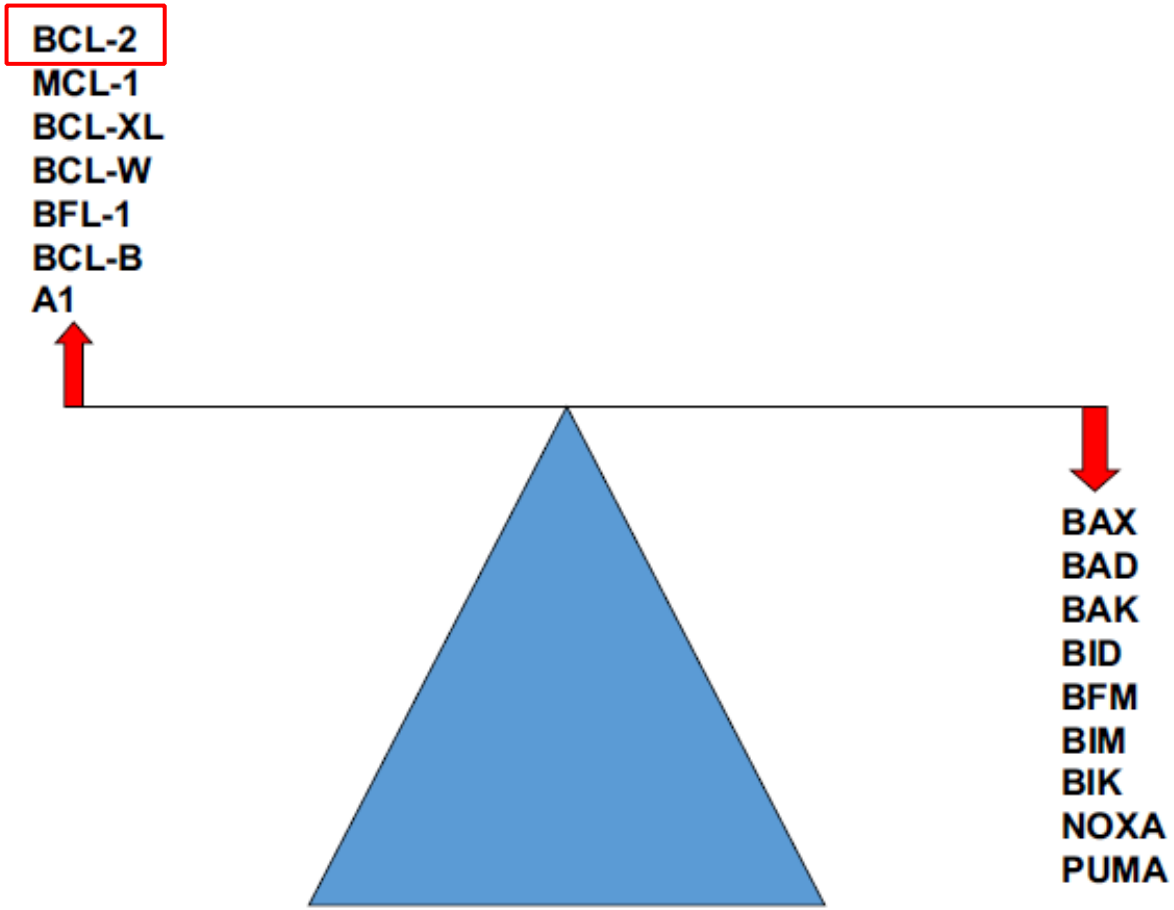
Gene regolatore dell'apoptosi

Contribuisce alla tumorigenesi bloccando la morte cellulare programmata (apoptosi)

Espressione deregolata sia come evento oncogenetico primario o secondario

Sviluppo del tumore | Mantenimento del tumore | Resistenza alla terapia

BCL-2 family of apoptotic proteins



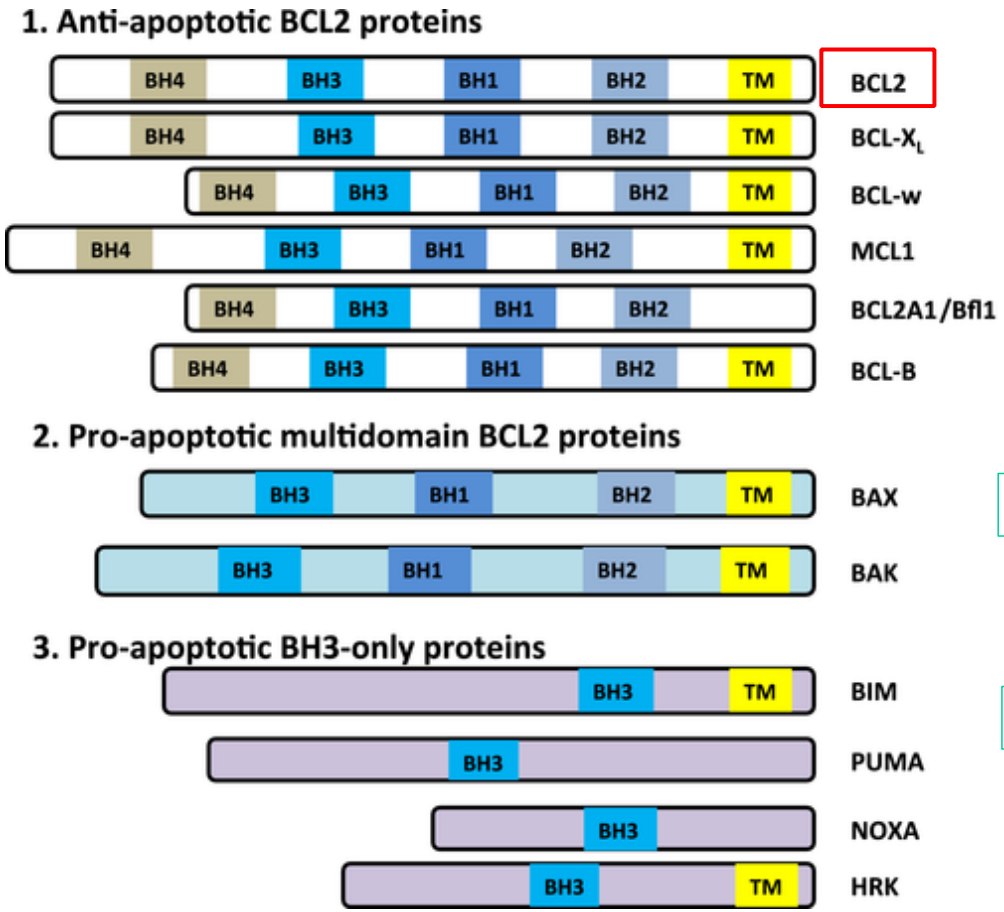
Fegan C and Pepper C, British Journal of Haematology, 2019

APOPTOSIS and BCL-2 family proteins

- Apoptosis (programmed cell death) is critical for normal development and homeostasis[a]
- The BCL2 family of proteins plays a major role in the intrinsic apoptosis pathway[b]
- Each protein contains up to 4 BCL2 homology (BH) regions (BH1, BH2, BH3, and BH4)[b]
- BCL2-family proteins regulate mitochondrial outer membrane permeability and release of cytochrome c, leading to caspase activation[b]

a. Leverson JD, et al. Cancer Discov. 2017;7:1-18
b. Taylor RC, et al. Nat Rev Mole Cell Biol. 2008;9:231-241
Kumar C, et al Blood 2017; 130:2401-2409

BCL2 family proteins

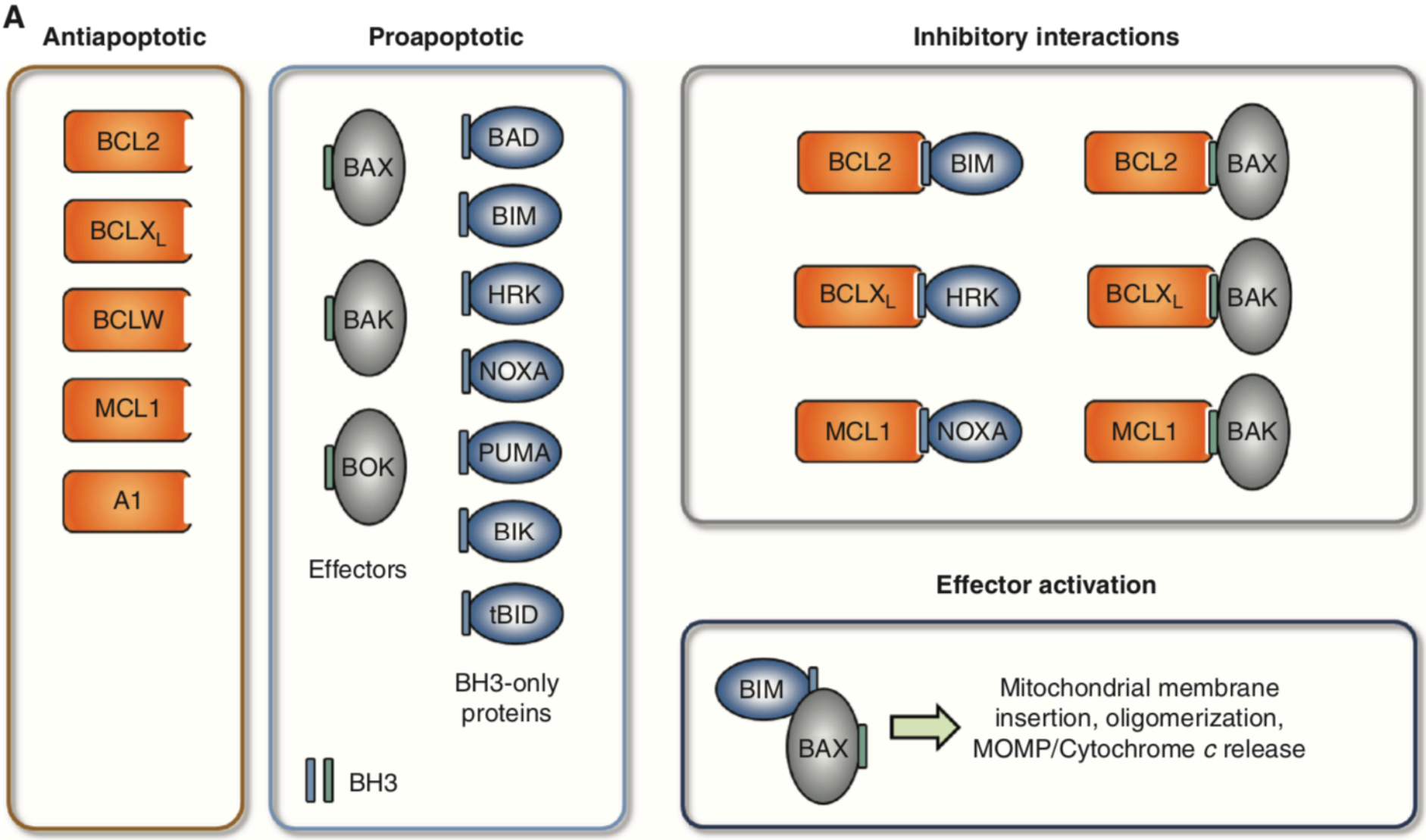


Effector proteins

Initiators proteins

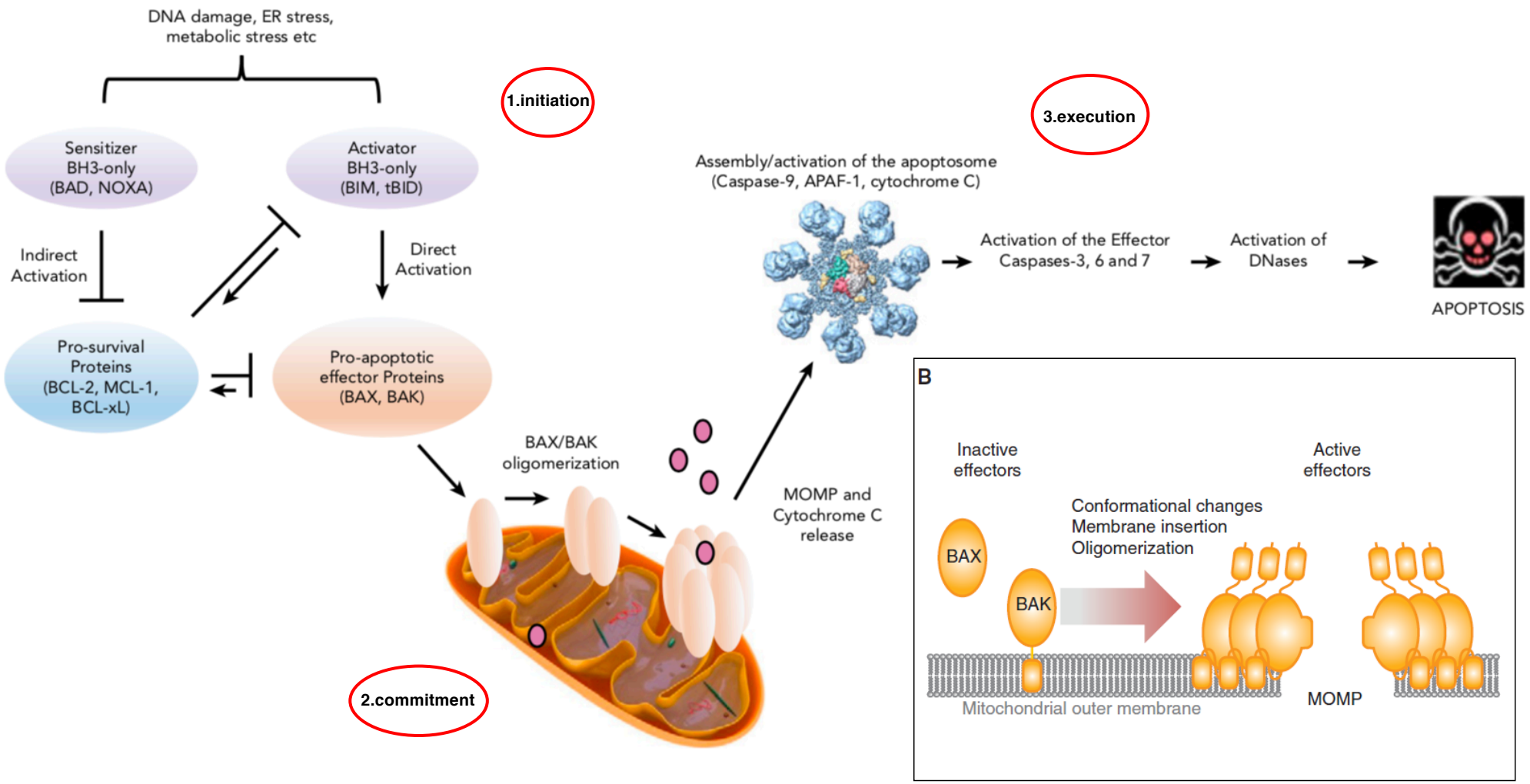
Voegler M, et al. British Journal of Haematology, 178:364-379

BCL2 family proteins



Leverson JD, et al. Cancer Discov. 2017;7:1-18

Intrinsec apoptotic pathway

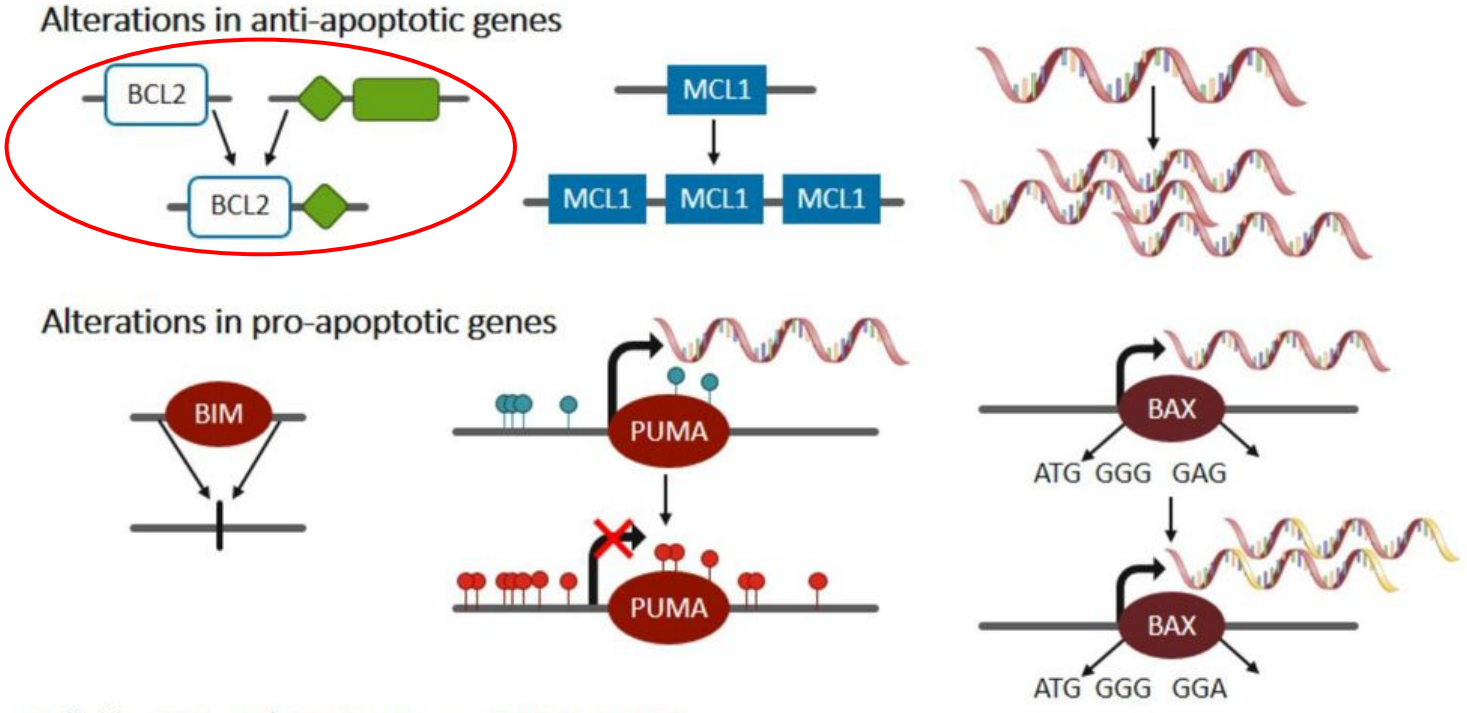


Valentin R, et al. Blood 2018;132:1248-1264

Green DR and Llambi F, Cold Spring Harb Perspect Biol 2015;7:1-24

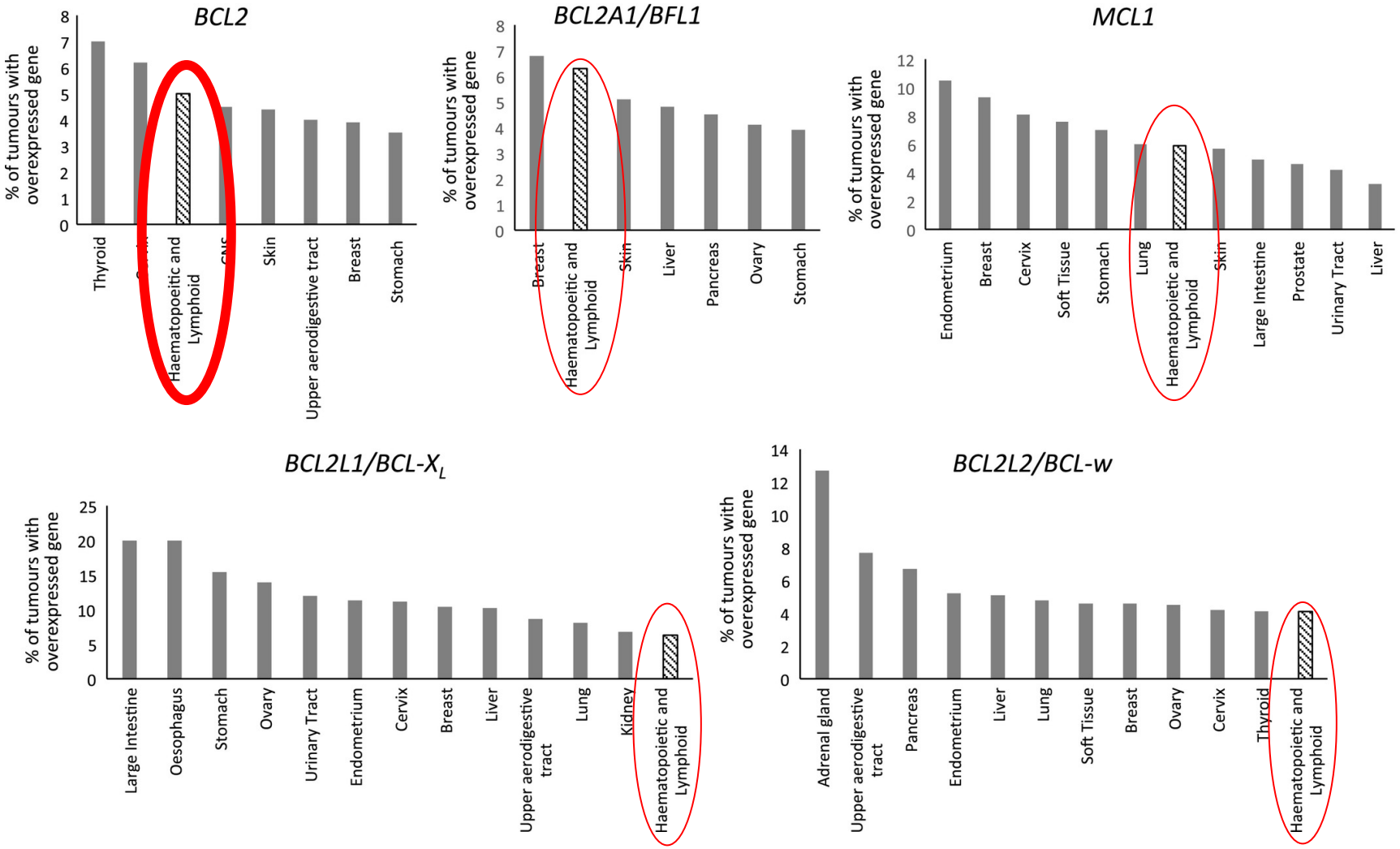
Mechanisms of BCL-2 family dysregulation

- Dysregulation of BCL2-family proteins plays a key role in cancer development



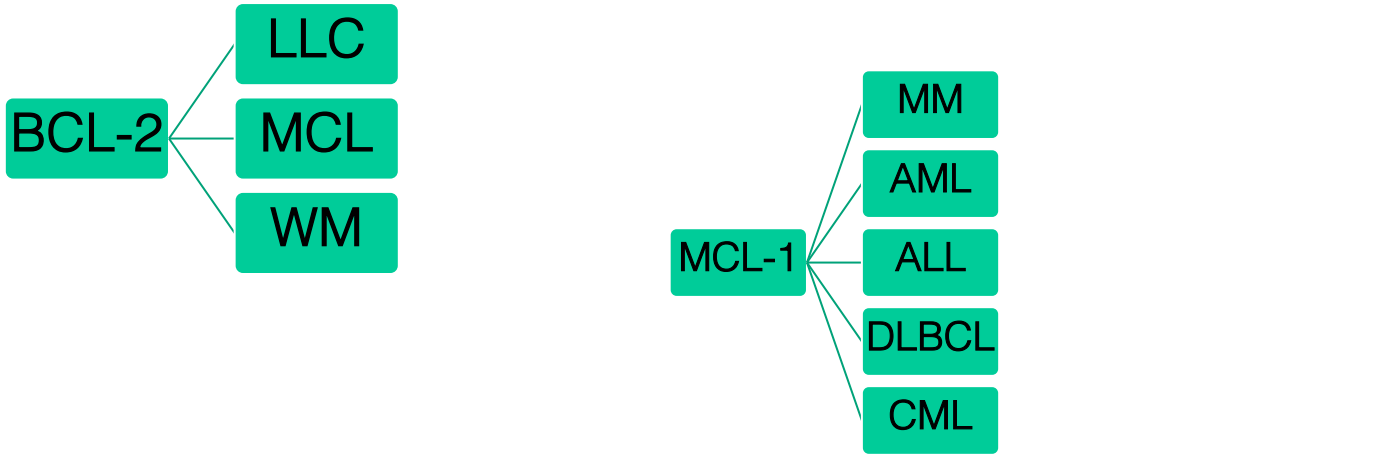
Delbridge ARD, et al., Nat Rev Cancer 2016;16:99-109

Overexpression of anti-apoptotic BCL-2 genes



Voegler et al., British Journal of Haematology,2017;178:364-379

BCL-2 family proteins



Valentin R, et al. Blood 2018;132:1248-1264

BCL-2/IGH t(14;18)(q32;q21)

BCL-2: gene driver del linfoma follicolare

presente nel 90% dei FL e nel 30% dei DLCL

marker citogenetico del linfoma follicolare

giustappone il locus delle catene pesanti delle Ig (14q32) al locus del gene BCL-2 (18q21)

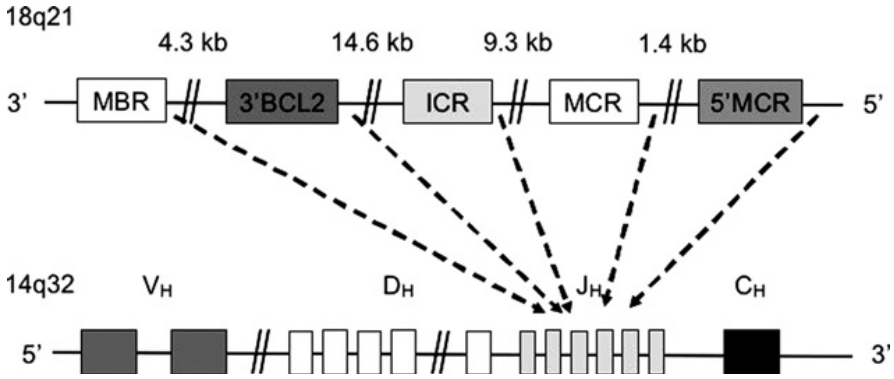
conseguente controllo trascrizionale sull'espressione della proteina

più rare le traslocazioni varianti: t(2;18)(p11;q21) e t(18;22)(q21;q21)

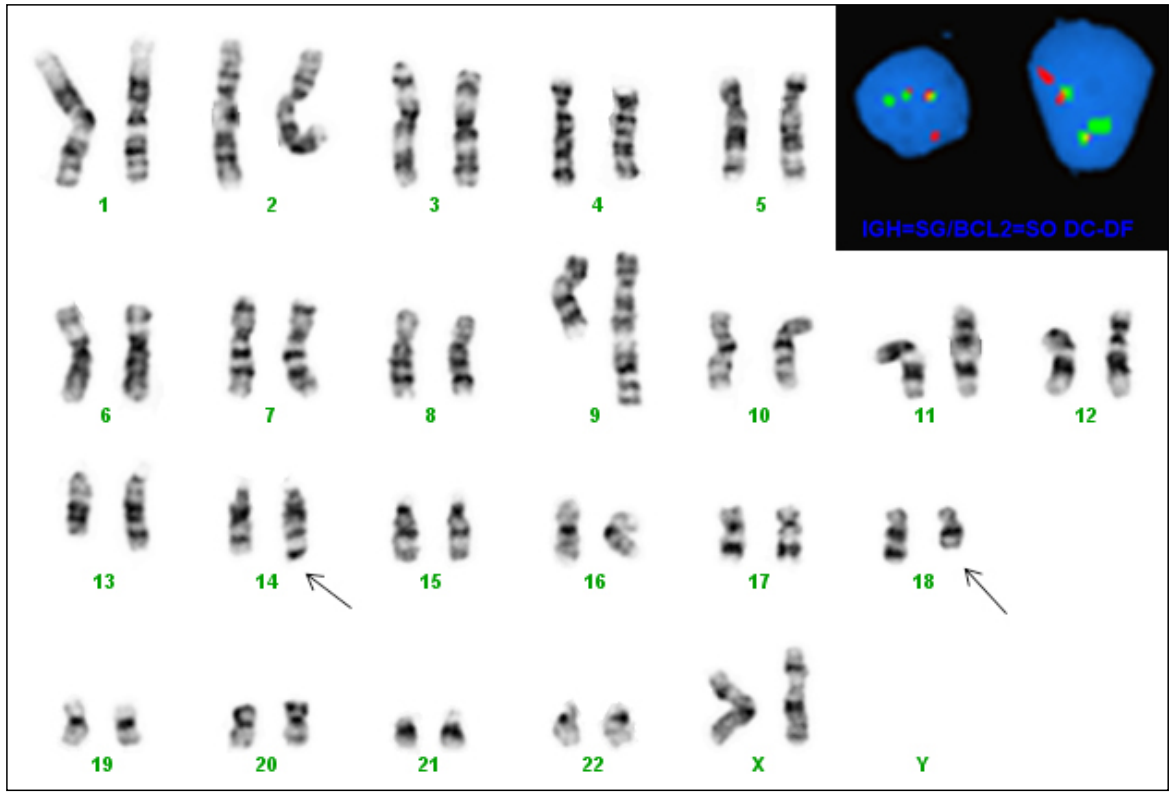
Major Breakpoint Region (MBR): 150 bp 3' al terzo esone BCL-2 (50-70%)

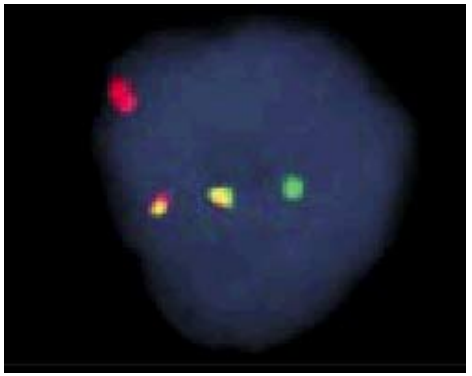
minor cluster region: regione a 20-30kb (circa 5%)

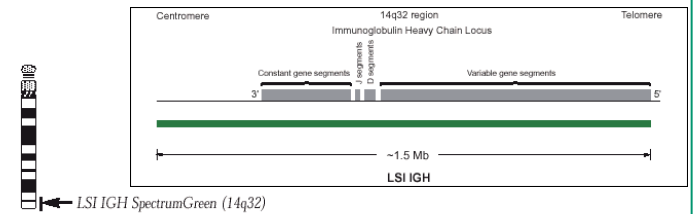
intermediate cluster region (icr) (circa 10%) – 3'BCL2 (6-10%)– 5' mcr (1-3%)

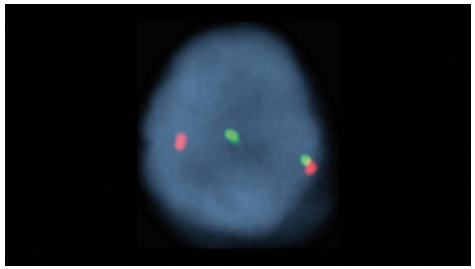


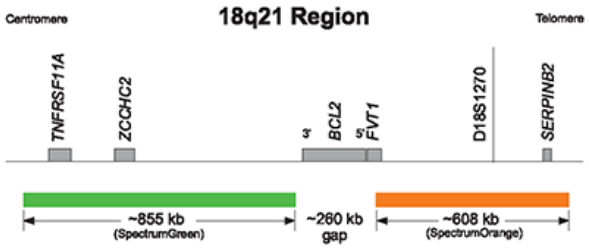
BCL-2/IGH t(14;18)(q32;q21)

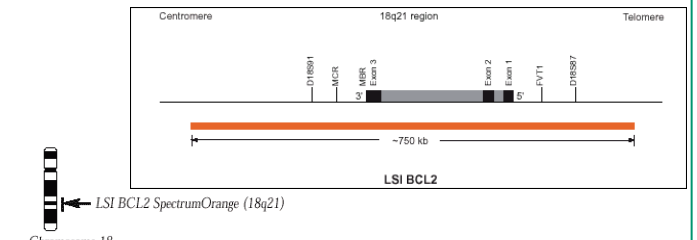












Double (Triple) Hit Lymphoma

2008 WHO Classification

Provisional Category:

"B-cell-lymphoma, unclassifiable, with features intermediate between DLBCL and BL"

Dual expression of MYC and BCL2 is now considered a negative prognostic indicator in *"DLBCL, NOS"*, but not a separate category!

MYC and BCL2 immunohistochemistry cannot be used as a surrogate marker for DH cytogenetic status:

- Most DH lymphomas are also DE but
- Most DE are not DH lymphomas!

2016 Update of 4th WHO Classification

New Category:

"High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (HGBL-DH/TH)"

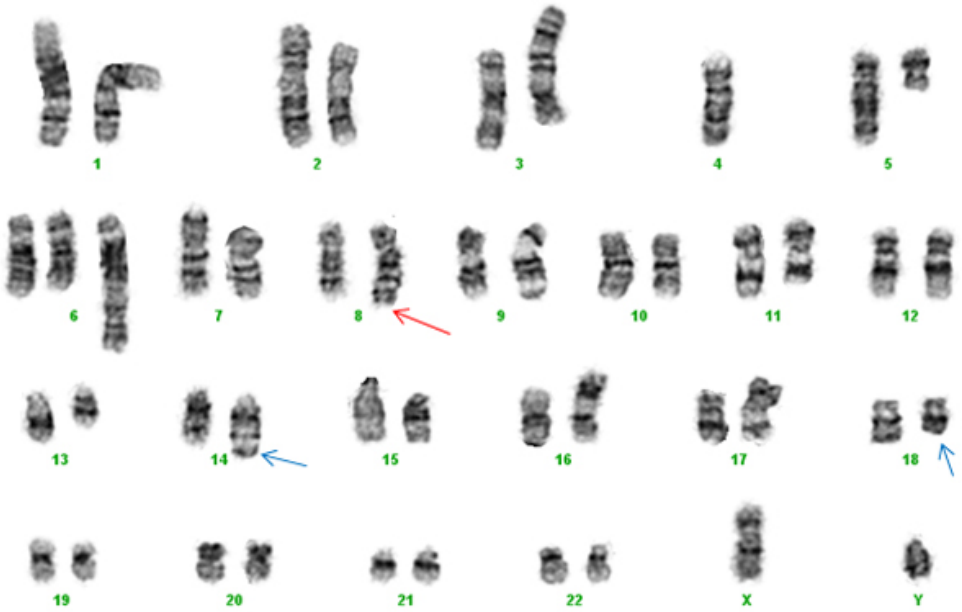
- Exclusively defined by presence of breakpoints/rearrangements!
- Not including high-level amplifications, CN alterations, protein expression!
- Not including low-grade follicular lymphomas with DH/TH

New Category:

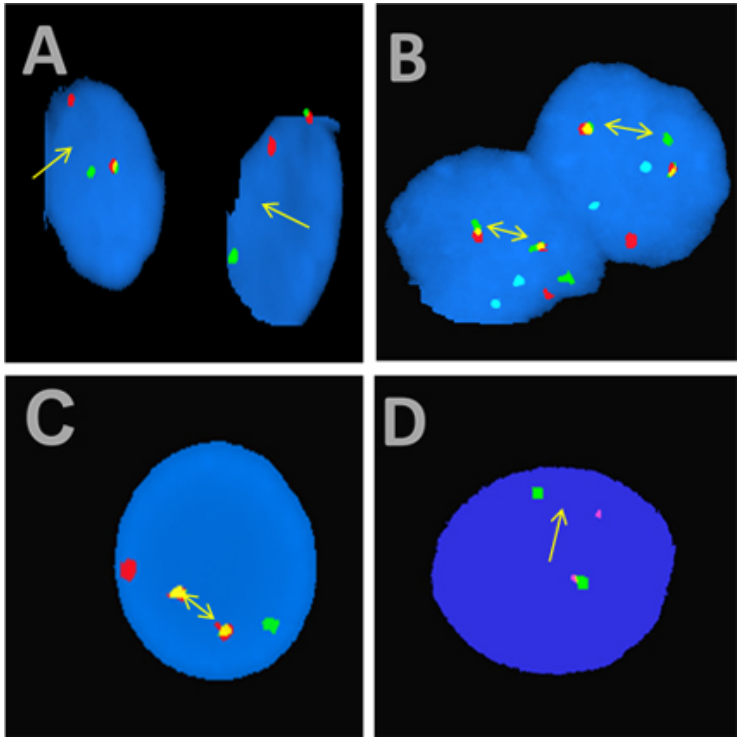
"High-grade B-cell lymphoma (HGBL), NOS"

- May carry isolated MYC rearrangements or BCL2 and/or BCL6 breakpoints
- Amplification of MYC may be seen
- Lymphomas with classical DLBCL morphology harboring isolated MYC translocation continue to be diagnosed as *"DLBCL"*

Linfoma Double (Triple) Hit
HGBL-DH/TH

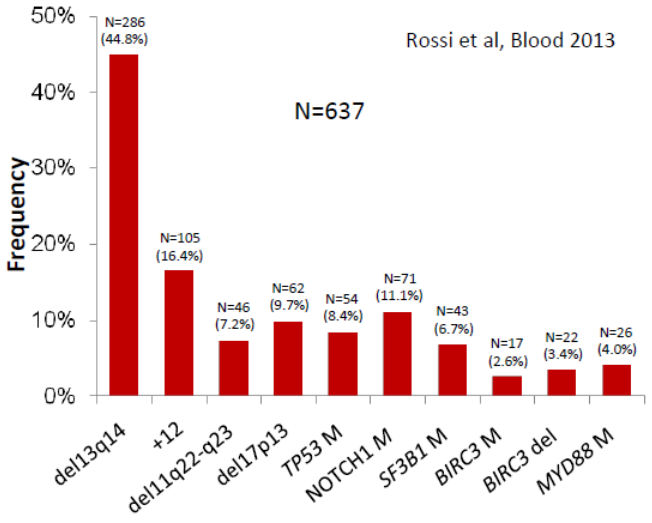


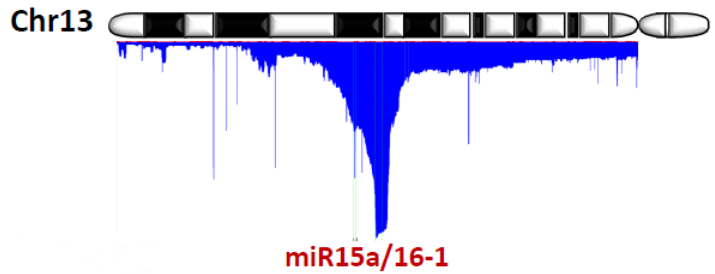
- spesso cariotipi complessi
- 2/3 casi doppia traslocazione con coinvolgimento di 8q24/MYC e t(14;18) con breakpoints in BCL-2
- meno comune traslocazioni di 8q24/MYC e 3q27/BCL6
- rari TH

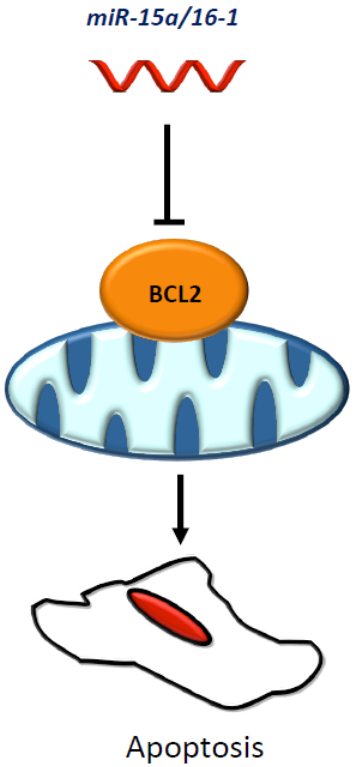


A) MYC ba
B) IGH/MYC, CEP8
C) IGH/BCL2
D) BCL6 ba

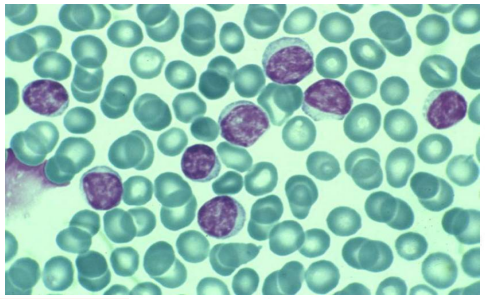
13q14 deletion: the most frequent genetic lesion in CLL

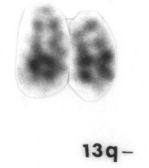




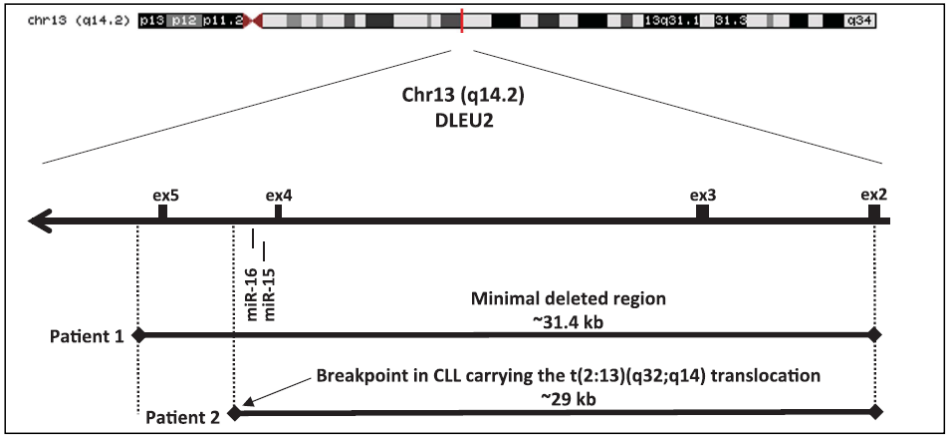


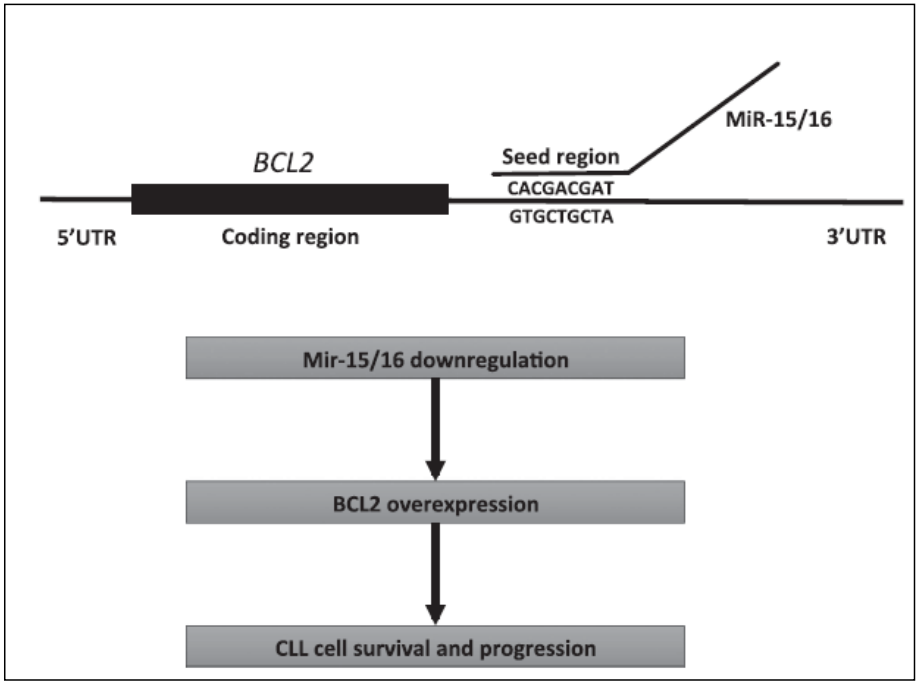
Cimmino et al, PNAS 2005





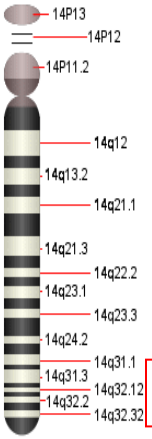
Deletion 13q and BCL-2





Pekarsky J, et al. 2018:25:21-26

Mieloma multiplo e traslocazioni (14)(q32)



- Circa 40% dei casi
- Coinvolgono la regione 14q32 con diversi partner cromosomici:

IGH

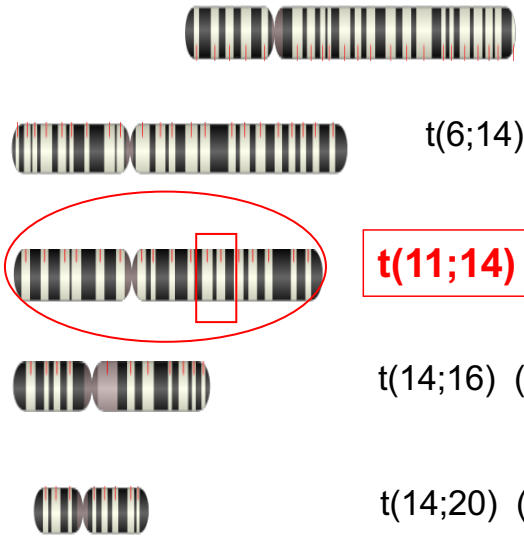
4p16 (FGFR3/MMSET) — t(4;14) (11-15% dei casi)

6p21 (CCND3) — t(6;14) (2% dei casi)

11q13 (CCND1) — **t(11;14) (15-20% dei casi)**

16q26 (c-MAF) — t(14;16) (5% dei casi)

20q12 (MAFB) — t(14;20) (2% dei casi)



t(6;14), t(11;14) fattori prognostici favorevoli.
t(14;16), t(14;20) fattori prognostici sfavorevoli
t(4;14) fattore prognostico intermedio.

Multiple myeloma, t(11;14) and BCL-2

Myeloma and t(11;14)

- 40% of myeloma patients have translocations, usually involving chromosome 14[a]
- Approximately 20% of myeloma patients have t(11;14)[a]
- t(11;14) is associated with intermediate risk[b,c]

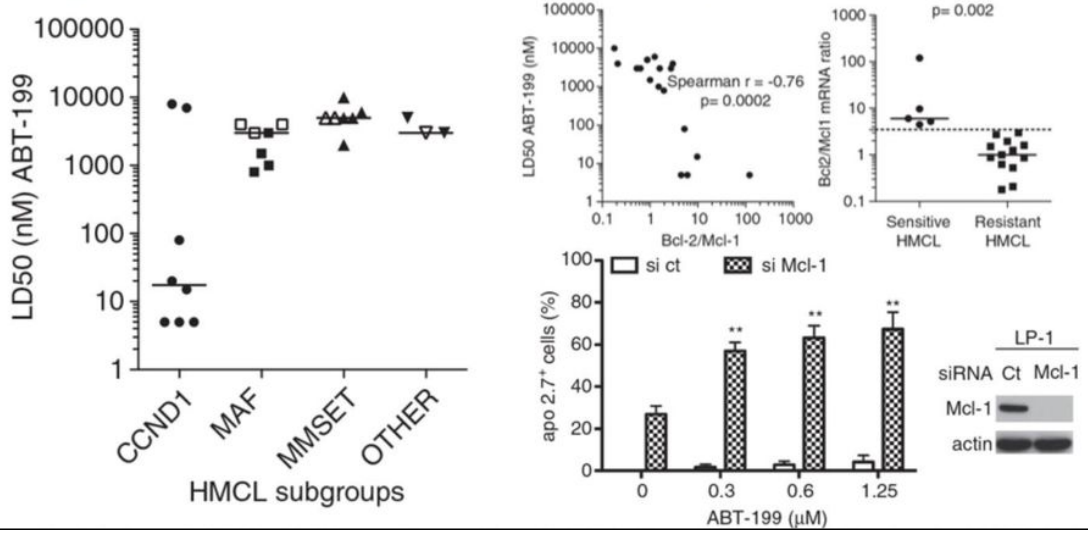
t(11;14) and BCL2 in Myeloma

- In myeloma cells, t(11;14) confers increased dependence on BCL2[d]
- BCL2 inhibition is particularly effective in myeloma patients with t(11;14)[e]
- Therefore, testing patients for the presence of t(11;14) may be particularly relevant when considering anti-BCL2 therapy

a. Avet-loiseau H,et al. Blood 2007;109:3489-3495
b. Lakshman A, et al. Leukemia 2017
c. Kaufman GP, et al.Leukemia 2016;30:633-639
d. Touzeau C, et al. Leukemia 2014;28:210-212
e. Kumar C, et al Blood 2017;130:2401-2409

BCL-2 inhibition and t(11;14)

- Myeloma cell lines with t(11;14) (CCND1 subgroup) were the most sensitive to BCL2 inhibition
- A high Bcl2/Mcl1 mRNA ratio indicates sensitivity to BCL2 inhibition

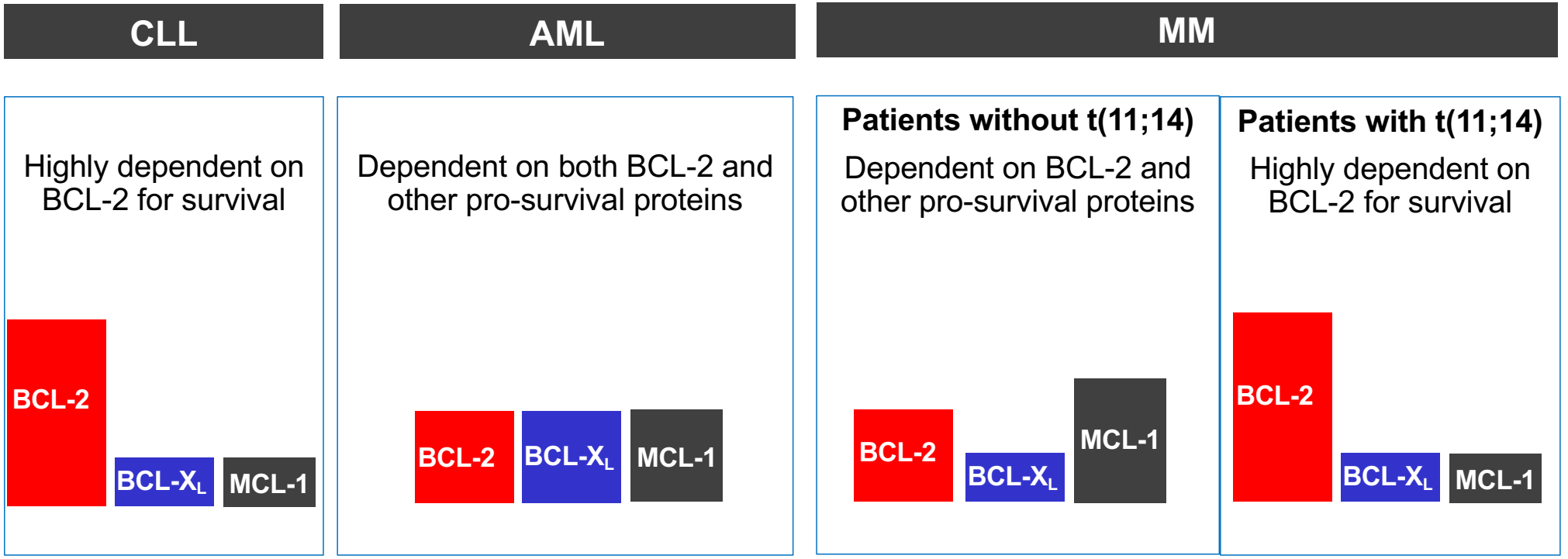


t(11;14)

- **Patients with t(11;14) are more likely to respond to anti-BCL-2 therapy**
- **High BCL-2/MCL1 and BCL-2/BCLX_L ratios indicate sensitivity to BCL-2 inhibition**

Kumar S,, et al Blood 2017;130:2401-2409
Majumder MM,et al. Oncotarget 2017;8:56338-56350

Malignant cells dependency on BCL-2 for survival across hematologic malignancies



Size of rectangles indicates relative dependency on specific protein for survival

Malignant cells' dependence on pro-survival proteins makes the BCL-2 family members rational targets for anti-cancer therapy

Gaidano G, Congresso Nazionale SIE 2019