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Molecular pathogenesis of Mantle Cell Lymphoma

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Introduction

Mantle cell lymphoma (MCL) is a B-cell neoplasm characterized by the expansion of mature B cells frequently co-expressing CD5 that tend to widely spread in bone marrow, blood, lymphoid tissues and extranodal sites. The tumor cells carry the t(11;14)(q13;q32) that leads to the constitutive overexpression of cyclin D1. In spite of this common initial oncogenic event, the tumors follow a very heterogeneous biological behavior indicating that other molecular mechanisms drive the evolution of the disease. The identification of two

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MCL subtypes, conventional and leukemic non-nodal, with different molecular characteristics and clinical manifestations may explain, in part, the diversity of the tumor. Recent genomic and molecular studies have expanded our perspective on the cell of origin and pathogenesis of these MCL subtypes. In this review we will address new findings on the MCL pathogenesis and the two molecular subtypes that may assist in the interpretation of the clinical diversity of these tumors.

Translocation t(11;14) and overexpression of Cyclin D1

The t(11;14)(q13;q32) is considered the primary oncogenic event in MCL development, virtually present in all cases, that juxtaposes *CCND1* at 11q13 with the IGH regulatory region leading to a constitutive overexpression of cyclin D1. The translocation occurs at the pro/pre-B stage of differentiation during the V(D)J recombination process and is mediated by recombination activating gene (RAG) enzymes.¹ The levels of cyclin D1 could be further increased by secondary rearrangements at the 3' of the gene or point mutations in the 3' untranslated region that create stable truncated cyclin D1 mRNAs.² This cyclin D1 overexpression may deregulate the G1/S cell cycle transition and promote the malignant transformation of B cells. Beyond its well characterized role in cell cycle, a number of growing evidences implicate cyclin D1 in additional cellular processes including transcriptional regulation by interacting with transcription factors, chromatin-remodeling elements, and histonemodifying enzymes.^{3,4} Cyclin D1 may also directly participate in DNA-damage response and apoptosis regulation.^{5,6} Interestingly, cyclin D1 binds to a high number of active promoters and interacts with the transcription machinery leading to a global transcriptome down-modulation in neoplastic lymphoid cells,⁷

Variant *CCND1* translocations and expression in MCL

A small subset of MCL cases show *CCND1* rearrangement with IGK or IGL light chain resulting in variant translocations t(2;11)(p11;q13)⁸ and t(11;22)(q13;q11.2)⁹, respectively, that determine similar cyclin D1 dysregulation. Intriguingly, recent studies have reported a minor subset of MCL that express cyclin D1 protein and high mRNA levels but *CCND1* rearrangements are not detected when evaluated by conventional cytogenetics or fluorescence in situ hybridization (FISH) using fusion or break-apart probes. Whole-genome sequencing (WGS) or FISH using custom bacterial artificial clones-labeled probes have detected that these cases carry cryptic rearrangements of IGK or IGL enhancers with *CCND1* gene which may be responsible for the cyclin D1 upregulation. The clinical and pathological features of this small subgroup of patients are similar to conventional MCL, suggesting that they correspond to the same molecular entity.^{10,11} This finding is in line with the identification by WGS of cryptic insertions of *MYC* into the IGH locus in IG-*MYC* negative Burkitt lymphoma cases,¹² or the detection of cryptic rearrangements involving *MYC* and *BCL2* in high grade B-cell lymphomas.¹³

Cyclin D1 negative MCL

A particular subset of cases with the same MCL morphology and phenotype lack cyclin D1 expression and t(11;14) translocation (cyclin D1⁻ MCL).¹⁴⁻¹⁶ These tumors have also

similar gene expression profile, secondary chromosomal alterations, and clinical behavior as cyclin D1⁺ MCL, suggesting that they correspond to the same disease.^{15–17} These cases should be distinguished from the uncommon MCL carrying the t(11;14) in which the cyclin D1 expression is not detected by immunohistochemistry due to mutations in the C-terminal domain of *CCND1* or the presence of *CCND1b* as the only expressed isoform that render the protein undetectable by current antibodies used in the pathology diagnostic routine.¹⁸

Initial FISH studies identified chromosomal rearrangements fusing *CCND2* with IG loci (IGH, IGK, or IGL) in 55% of cyclin D1⁻ MCL.¹⁵ However, the primary oncogenic event remained elusive in a substantial fraction of these cases. More recently, next generation sequencing (NGS) studies and FISH with custom probes have found the insertion of a small IGK region including its enhancer near *CCND3* (16%) or *CCND2* (7%), leading to cyclin D3 or cyclin D2 overexpression, respectively. Similar cryptic insertions involving the IGL-enhancer in the vicinity of *CCND3* associated with cyclin D3 overexpression have been also detected in a subset of cyclin D1⁻ MCL. Overall, 23% of the cyclin D1⁻ MCL cases showed an IG light chain enhancer hijacking as initial oncogenic event.¹⁹

SOX11: the key oncogenic factor

SOX11 is a transcription factor that plays an important oncogenic role in MCL pathogenesis through its impact in B-cell differentiation, tumor microenvironment interactions, cell cycle control and apoptosis.^{20,21} SOX11 is not expressed in normal lymphoid cells or other mature B cell lymphomas with the exception of 25–50% of Burkitt lymphoma, but it is highly expressed in conventional MCL, including cyclin D1⁻ MCL.¹⁷ Hence, SOX11-nuclear staining is a useful tool in the differential diagnosis of MCL and other small B-cell neoplasias. SOX11 may contribute to MCL pathogenesis by the constitutive activation of PAX5, a master regulator of B cell development, that blocks terminal B-cell differentiation and promotes tumor growth.²¹ Another SOX11 direct regulated target is BCL6, an essential element for B-cell development and maintenance of follicular germinal centers (GC). SOX11 may block BCL6 expression preventing the entrance of MCL cells in the GC.²⁰ The transgenic mouse model (E μ SOX11-EGFP) developed by Kuo *et al.* shows hyperactivation of pBTK and other molecules of the BCR signaling pathway driving tumor development.²² Moreover, SOX11 regulates interactions of MCL cells with the microenvironment inducing angiogenesis through PDGFA²³ and promoting tumor cell migration, adhesion, and cell proliferation by upregulating CXCR4 and FAK.²⁴ Accordingly, treatment *in vitro* of MCL cells with FAK inhibitors could overcome ibrutinib resistance.²⁵

In spite of the relevant role of SOX11 in MCL the mechanisms leading to its specific upregulation in this lymphoma are not well understood. Recent studies have suggested that SOX11 expression in these cells could be mediated by epigenetic mechanisms that alter the 3-dimensional configuration of chromatin bringing together a distant active enhancer region with the promoter of the gene.²⁶

MCL molecular subtypes: distinct pathogenic pathways

The initial translocation t(11;14)(q13;q32) may be followed by two distinct pathogenic pathways resulting in two subtypes of tumors with different biological behavior. The most common subtype is the conventional MCL (cMCL), that derives from a cell that does not enter into the follicular GC and carry no or a limited number of IGHV somatic mutations (Figure 1).²⁷ The second subtype, leukemic non-nodal MCL (nnMCL), derives from a cell that has gone through the GC acquiring IGHV somatic mutations.²⁸ These two subtypes have different cellular origin, a naive-like B-cell for cMCL and an experienced GC memory-like B cell for nnMCL. This idea is supported by the observation that both subtypes retain the DNA methylation pattern of their normal cellular counterparts.^{26,28}

Although cMCL and nnMCL share similar global gene expression profiles, they differ in some genetic and molecular characteristics. cMCL cases overexpress SOX11, are genetically unstable and tend to accumulate many chromosomal alterations. Clinically, patients with cMCL usually have generalized lymphadenopathy at diagnosis and follow an aggressive clinical course.^{29–30} Contrarily, nnMCL present an initial indolent disease that may be stable for long periods of time. Patients have leukemic involvement with minimal lymphadenopathy and later on may develop splenomegaly.^{31–35} These cases might benefit of a careful observation management without negatively impacting their outcome.^{36–39} Although nnMCL cells initially harbor few or no chromosomal alterations besides the t(11;14), they may evolve over time acquiring *TP53* mutation, 17p loss and increased genome instability that confer a dismal prognosis.³⁴ Recently, a 16-gene assay on the NanoString platform (L-MCL16 assay) has been used to classify patients with leukemic involvement into cMCL or nnMCL subgroups and, in combination with genomic complexity and *TP53* alterations, predict patients' outcome.³⁵

From early lesions to an overt lymphoma

The oncogenic steps from the early *CCND1* rearrangement to the development of an overt lymphoma are not well known. The detection of cells carrying the t(11;14) in the peripheral blood of 8% of healthy individuals suggests that not all the cells acquiring the initial translocation will evolve into a malignant lymphoma.³⁶ These clones may persist for long latency periods prior to evolve into a malignant neoplasm as supported by the observation of a simultaneous MCL with the same clonal origin in the recipient and donor 12 years after an allogenic bone marrow transplantation.³⁷

Cyclin D1 positive cells are occasionally found in the inner mantle zone of reactive lymphoid follicles, a situation now known as *in situ* mantle cell neoplasia (ISMCN) (Figure 1). These *in situ* lesions are usually identified incidentally and sometimes in association with other lymphomas.^{38,39} Although some of these cases may affect different territories the patients have a long-term follow-up without developing progressive disease in the absence therapeutic intervention. The proportion of ISMCN that may develop an overt lymphoma is not well known but seems very low.⁴⁰ However, some patients with these lesions may have already a disseminated MCL at diagnosis and therefore they should be explored carefully to rule out this situation (Figure 1).

The hallmarks of cancer in MCL

The concept of cancer hallmarks helped to dissect the malignant phenotypes that are associated with specific physiological circuits dysregulated during the oncogenic process.⁴¹ The order in which the different neoplasias acquire their hallmarks capabilities and their contribution during oncogenesis depends on the type of tumor. In MCL, the t(11;14) translocation responsible of cyclin D1 dysregulation would represent the initial acquisition of a sustained proliferative signaling. However, this event is not sufficient to explain the MCL pathogenesis. Secondary genetic alterations would reinforce the proliferation dysregulation and promote the acquisition of additional hallmarks relevant to MCL lymphomagenesis (Figure 2).

1. Sustaining proliferative signaling and growth suppressors evasion

An essential feature of tumor cells is their capacity for continuous proliferation together with the ability to circumvent the constrain proliferation promoted by tumor suppressors under cell stress conditions. In MCL, the initial dysregulation of cyclin D1 may promote G1/S phase transition through the binding of the cyclin to CDK4, followed by RB1 phosphorylation, and subsequent E2F release. Besides this initial alteration, secondary genetic events also impact directly in cell cycle control affecting mainly two pathways INK4A/CDK4/RB1 and ARF/MDM2/TP53. The 12q13 amplification (20%) may led to CDK4 overexpression that would further promote cell cycle dysregulation.⁴² Interestingly, the inhibition of CDK4 can be a reliable mechanism to overcome the ibrutinib resistance in MCL patients.⁴³ The 9p21 deletion (25%), involving the *CDKN2A*, is one of the most frequent genetic alteration in MCL. *CDKN2A* gene encodes for p16 (*INK4A*), a cyclin dependent kinase inhibitor that specifically inhibits CDK4 and CDK6 keeping RB1 active, and for p14 (*ARF*), a E3 ubiquitin-protein ligase that stabilize p53 by interacting with MDM2 preventing its degradation.⁴² Alternatively, few MCL cases with wild-type *CDKN2A* show *BMI1* (10q13) amplification and overexpression which act as a transcriptional repressor of the *CDKN2A* locus.⁴⁴ Inactivation of *CDKN2A* is associated with an unfavorable prognosis in MCL patients and is related to aggressive variants.⁴⁵ Similarly, inactivation of *RB1* by mutations and homozygous deletion, although uncommon, occurs mainly in aggressive cases.⁴⁶ Other genetic alterations targeting cell cycle related genes that might confer increased proliferation rates are *MYC* amplification and translocation,^{44,47} and deletions of *CUL4A* and *ING1* (13q34).⁴⁸

The high number of genetic alterations that potentially dysregulate cell cycle in MCL underscores the relevance of this hallmark in MCL pathogenesis. Moreover, its relevance is supported by the fact that the best predictor of patient survival in MCL is a proliferation gene expression signature that may integrate the multiple genetic alterations dysregulating cell cycle and may now be reliably determined in formalin fixed paraffin embedded tissues (MCL35 proliferation assay).^{49,50}

2. Genomic instability

Cancer cells have a tendency to accumulate genetic alterations and increased genomic instability, a hallmark of many tumors. MCL is one of the B-cell malignancies with highest

degree of genomic instability. More than 90% of the MCL cases display highly altered genomes, with gains/amplifications and homozygous/heterozygous losses, as well as other non-recurrent chromosomal rearrangements. Losses in 1p, 6q, 8p, 9p, 9q, 10p, 11q, 13q, and 17p and gains in 3q, 7p, 8q, 10p, 15q and 18q are the most frequent chromosomal alterations identified in MCL.⁵¹ The high number of chromosome alterations in MCL cells is consistent with the fact that the two most common mutated genes are *ATM* (40–50%) and *TP53* (21–45%), both involved in DNA damage response. *ATM* alterations, including mutations and 11q deletions, are considered early events but do not correlate with prognosis, despite being related to increased chromosomal instability⁵². Downregulation of *CHK2* and *CHK1*, two critical serine-threonine kinases involved in signal transduction during DNA damage response, may constitute another mechanism to promote chromosome instability in a limited number of MCL cases.⁵³ *TP53* is frequently inactivated by point mutations and 17p13 deletion, compromising the p53-mediated cell cycle arrest, apoptosis and senescence as response to DNA damage. *TP53* alterations are identified at similar proportion in cMCL and nmMCL. Additionally, the increased number of chromosomal imbalances, *TP53* mutations and global genetic instability are associated with blastoid variants and worse clinical outcome in MCL patients.^{35,54–56}

3. Resisting cell death

The evasion of apoptotic cell death, considered a natural barrier to cancer development, is a key hallmark of cancer cells. In MCL, dysregulation of the antiapoptotic protein *BCL2* mainly by amplifications or mRNA overexpression is described in 3–17% of cases. Upregulation of other proteins of the *BCL*-family, like *BCLX*, as well as occasional biallelic loss of the proapoptotic *BCL2L11* (2q13) have been also observed.⁵⁷ In the last decade, several reports have described recurrent gain-of-function truncating mutations in *NOTCH1* (5–14%) and *NOTCH2* (5%) associated with blastoid variants and dismal prognosis.^{58,59} *NOTCH* pathway is one of the most evolutionary conserved signaling cascades across species that regulates cell death but also cell proliferation and activates specific differentiation programs.⁶⁰ *NOTCH* signaling regulates, directly or indirectly through *MYC*, a gene signature consisting of *BCR* signaling, RNA metabolism and chromatin/transcriptional modulation. Clinically, *NOTCH* targeted approaches may be a therapeutic option for a subset of patients.⁶¹

4. Modulation of tumor microenvironment interactions

Normal B-cell maturation involves somatic recombination and mutation of the *IGHV* genes that encode the antigen binding domains of the B cell receptor (BCR). The observation of restricted repertoires of *IGHV* genes in MCL, called BCR IG stereotypy, highlights the antigen selection and BCR signaling pathway as important hallmark for MCL pathogenesis.⁶² Additionally, constitutive activation of the BCR signaling pathway has a key role promoting survival and proliferation of the malignant B cells. Although the specific mechanisms involved in this deregulation are not well understood, different B-cell receptor associated kinases including tyrosine protein kinase (*LYN*), spleen tyrosine kinase (*SYK*)⁶⁹, and especially Bruton's tyrosine kinase (*BTK*) are considered therapeutic targets due to their constitutive activation or amplification in MCL. In this context, the oral covalent inhibitor of *BTK* ibrutinib, shows durable single-agent efficacy in MCL cases.⁶³ Recently, in the

MCL-0208 trial, high expression levels of a 6-gene BCR signature (*AKT3*, *BCL2*, *BTK*, *CD79B*, *PIK3CD*, and *SYK*) was associated with shorter progression-free survival and OS.⁶⁴

The constitutive activation of PI3K/AKT and NF- κ B signaling pathways also play a relevant role in MCL pathogenesis. Activated PI3K/AKT/mTOR components target a wide range of downstream processes in MCL, including angiogenesis but also cell survival, growth, and protein synthesis. Activation of downstream kinases such as SYK and *PI3KCA* amplification may cause activation of this pathway and can determine the therapeutic potential of small molecule inhibitors.⁶⁵ The activation of the canonical NF- κ B pathway directly correlates with increased tumor proliferation and inferior survival in MCL.⁶⁶ The NF- κ B activation can be mediated by different alterations, mainly by inactivating mutations or deletions in negative regulators as *TNFAIP3/A20*,⁶⁷ *TRAF2*, *BIRC3*, *NFKBIE*, and *CARD11*. *NFKBIE* deletions are associated with poor outcome,⁶⁸ meanwhile *TRAF2* and *BIRC3* mutations are associated with resistance to ibrutinib therapies in MCL.⁶⁹ The antiapoptotic proteins BCL-2, BCL-X_L, XIAP and cFLIP, are also NF- κ B targets highly expressed in MCL.^{70,71}

Additionally, during tumor progression the ability to sprout new blood vessels must be kept intact. Experimental studies have shown that SOX11 expression is associated with an angiogenic switch through PDGFA activation and is characterized by increased expression of angiogenic-related signatures and vascularization.^{23,72} Interestingly, SOX11 directly regulates CXCR4 and PTK2 conferring a protective microenvironment-related signatures in SOX11+ MCL cases. CXCR4 and CXCL12 overexpression enhance FAK activation promoting MCL cell migration and adhesion facilitating the crosstalk with the stromal cells that confers survival and drug resistance to MCL cells.²⁴

5. Epigenetic dysregulation

Epigenetic dysregulation can promote malignant cellular transformation and is considered a hallmark for a large number of different neoplasms. In the last years, the characterization of whole tumor cell methylomes confirmed the critical role that DNA methylation plays in MCL tumorigenesis and it was identified as a dynamic process prone to be altered upon neoplastic transformation. In MCL cells, an increased DNA methylation burden, defined as the number of methylation changes acquired by tumor cells, is associated with worse clinical outcome and higher number of driver mutations.²⁶ Moreover, the genomic analysis of MCL has revealed that epigenetic modulators are recurrent altered targets. The most frequently mutated epigenetic modifier in MCL is *KMT2D* (17–23%), a regulator of transcriptional and posttranslational processes which mutations may have impact on the outcome of patients.⁵⁵ Mutations in the catalytic domain of the *NSD2* are also found in cMCL and are associated with overexpression of signatures related to proliferation and cell cycle, as well as with global chromatin methylation driving oncogenic reprogramming in other lymphoid malignancies.^{73,74} Recently, *NSD2* has been described to mediate dimethylation of PTEN and facilitate its recruitment into DNA-damage sites contributing to the repair of DNA double strand breaks.⁷⁵ Moreover, alterations in SWI-SNF chromatin remodeling complexes, including *SMARCA4* mutations (5–12%) or deletions involving *SMARCA2*

(9p24) or *ARID2* (12q12) confer resistance to ibrutinib and venetoclax.⁷⁶ Other dysregulated epigenetic modifiers are *KMT2C* (5–16%), *BMI1* (6–12%), and *TET2* (5–12%). Finally, mutations targeting regulators of transcription such as *MEF2B* (3–7%) or posttranscription *UBR5* (7–18%) are also recurrently found in MCL.^{58,77}

Summary

The translocation t(11;14) is the genetic hallmark of MCL although cryptic rearrangements of IG regulatory regions could be an alternative oncogenic mechanism in a minor subgroup of patients. Interestingly this IG enhancer hijacking phenomenon is found recurrently in MCL cyclin D1⁺ cases with cyclin D2 or cyclin D3 overexpression. MCL is considered one of the most aggressive lymphomas. However, a small subset of cases may follow an initial indolent clinical course without need of treatment. The presence of IGHV somatic mutations, leukemic expression in the absence of lymphadenopathies, as well as, low number of genomic alterations are characteristics that differentiate nmMCL from cMCL cases. The dysregulation of cyclin D1, although considered the primary oncogenic event, is not enough for malignant transformation of B-cell clones. In this sense, additional somatic genetic alterations affecting genes involved in many cancer hallmarks, like cell cycle control (*CDKN2A*, *CDK4*, and *RB1*), DNA damage response (*TP53*, *ATM*, *CDKN2A*, and *MYC*), epigenetic modulation (*KMT2D*, *SMARCA4*, and *NSD2*) and NF-κB signaling pathways (*BIRC3*, *NFKBIE*, and *TNFAIP3*) among others, may impact MCL lymphomagenesis. Additionally, *SOX11* seems to collaborate with cyclin D1 in MCL pathogenesis, regulating a complex transcriptional program and enhancing the aggressiveness of the tumor. The better understanding of MCL pathogenesis generated by the use of NGS technologies and the integration of multidisciplinary research, from molecular biology and pathology to the clinic, has revealed new potential management strategies for the treatment of aggressive MCL.

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Key Points

- Cryptic translocations of IG enhancers near *CCND1*, *CCND2* and *CCND3* represent an alternative mechanism to the t(11; 14) as an initial oncogenic event in MCL.
- The leukemic non-nodal MCL subtype displays different clinicobiological features and better outcome than conventional MCL.
- SOX11 is an oncogenic transcription factor highly expressed in conventional MCL with a relevant role in its pathogenesis, but its regulation is poorly understood.
- Next generation sequencing studies have provided new insights into the molecular MCL pathogenesis and have helped to refine the MCL cancer hallmarks.

Synopsis

Mantle cell lymphoma (MCL) is a mature B-cell neoplasm with heterogeneous clinical behavior that is molecularly characterized by the constitutive overexpression of cyclin D1 and deregulation of different signaling pathways. SOX11 expression determines an aggressive phenotype frequently associated with the accumulation of high number of chromosomal alterations and somatic gene mutations. A subset of patients with the SOX11-negative leukemic non-nodal MCL subtype follows an initial indolent clinical evolution and may not require treatment at diagnostic, although eventually may also progress to an aggressive disease. In this review, we discuss the genetic and molecular alterations with impact on the cancer hallmarks that characterize the lymphomagenesis of the two MCL subtypes.

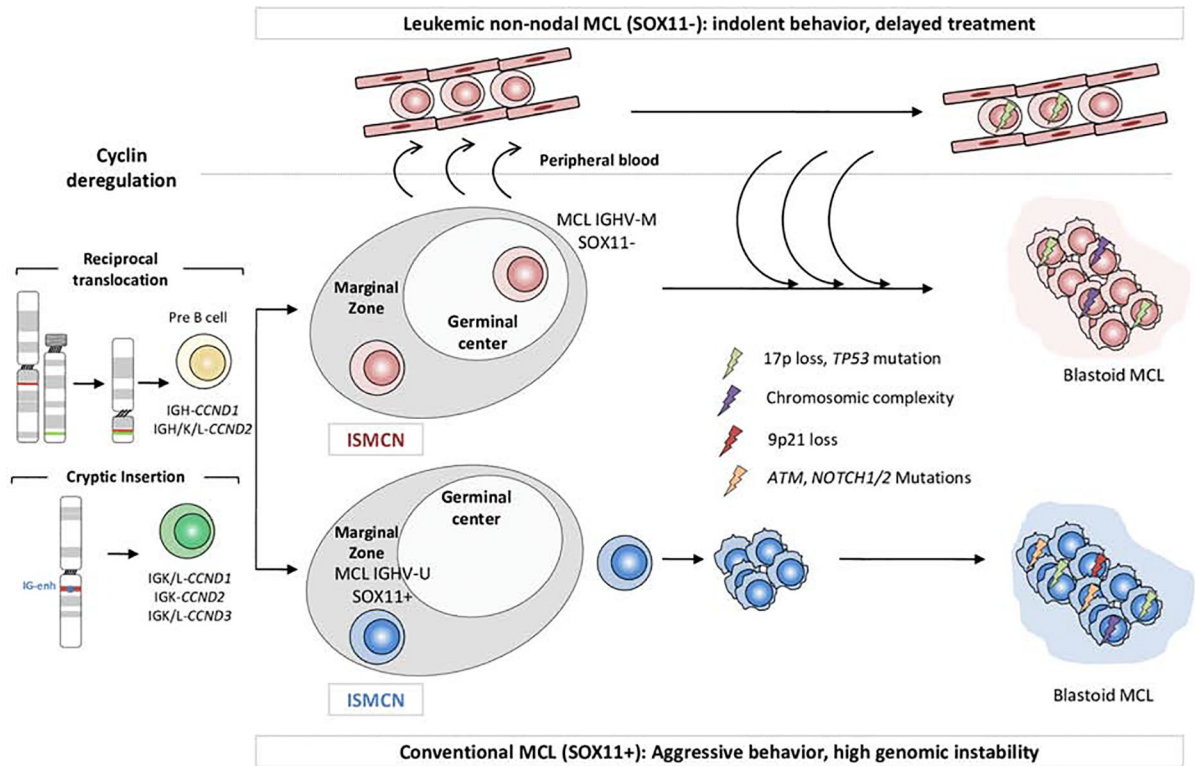


Figure 1. MCL molecular subtypes.

The naïve B-cell with cyclin deregulation may evolve into two distinct molecular subtypes with different molecular and clinicopathological characteristics.

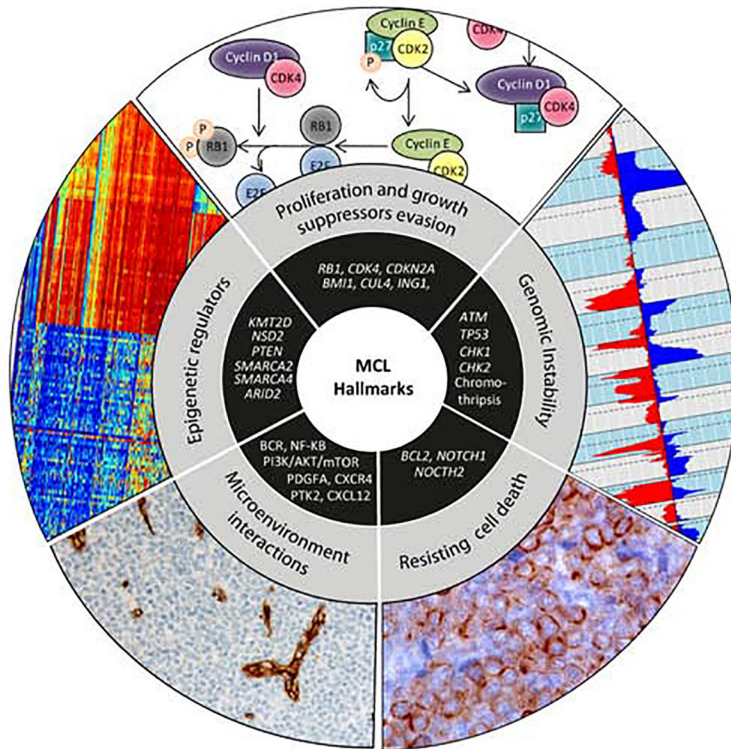


Figure 2. MCL hallmarks.

The conceptual framework encompasses many different cellular functions that transform normal cells into malignant cancer cells. All the related pathways involved in MCL pathogenesis may be globally grouped into five main hallmarks.