Genetics of Blastic Plasmacytoid Dendritic Cell Neoplasms

Subjects: Hematology

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Differential diagnosis between Blastic pDC Neoplasm (BPDCN) and Acute Myeloid Leukemia with pDC expansion (pDC-AML) is particularly challenging, and genomic features can help in diagnosis. The genetic landscape of BPDCN is now well-defined, with important updates concerning MYC/MYC rearrangements, but also epigenetic defects and novel concepts in oncogenic and immune pathways.

mature plasmacytoid dendritic cells proliferation | acute myeloid leukemia | RUNX1 mutation

1. Genetics of Blastic Plasmacytoid Dendritic Cell Neoplasms

Cytogenetic abnormalities are detected in 57 to 75% of BPDCN patients. Most of the karyotypes contain a wide spectrum of cytogenetic abnormalities, leading to a complex karyotype (CK) (≥3 aberrations) in more than 50% of cases [1][2]. Abnormal karyotypes of BPDCN show a high number of aberrations (mean = 6.8 per case). Using conventional cytogenetic and Fluorescent In Situ Hybridization (FISH)/multi-FISH approaches, a special and distinct cytogenetic signature of BPDCN have been described, showing various but recurrent chromosomal losses or deletions over gains. These abnormalities include 6 major recurrent chromosomal losses detected at high frequency among abnormal karyotype: 5q deletion (72%), 12p deletion (64%), 13q deletion or monosomy 13 (64%), 6q deletion (50%), 15q deletion or monosomy 15 (43%), and monosomy 9 (28%) [1]. Remarkably, among CK, careful examination revealed that three or more of these six chromosomal targets were associated in 50% of cases, defining a special cytogenetic signature for BPDCN. These results have been confirmed by two independent studies [3][4].

These recurrent deletions were confirmed by chromosomal microarrays analyses, with losses of 9p21.3 (*CDKN2A/CDKN2B*), 12p13.2-p13.1 (*CDKN1B*, *ETV6*), 13q11-q21 (*LATS2*, *RB1*), 5q31 (*NR3C1*), or 7p12.2 (*IKZF1*) [1][2][5]. Despite this original pattern of recurrent abnormalities, there is no unique key genetic event in BPDCN. Indeed, at least four genes are particularly deleted and/or mutated: *IKZF1*, required for BPDCN differentiation [6]; *RB1*, potentially associated with transformation in the case of biallelic inactivation [7], *ETV6*, whose deletion would correspond to an early pathogenic event [4], and *NR3C1*, involved in the glucocorticoid metabolism [3]. The transcriptional activators *MYC* and *MYB* are also originally rearranged at high frequency in this neoplasm. Remarkably, the significant association of these alterations (i.e., loss of *CDKN2A-B*/9p21, *CDKN1B*/12p13, or *RB1*/13q14, rearrangement of *MYC*/8q24 or *MYB*/6q23) constitute the special and unique pattern frequently detected in BPDCN.

2. Genetics of Blastic Plasmacytoid Dendritic Cell Neoplasms

2.1. Deletions Involving Immune Genes

Interestingly, these recurrent deletions also involve genes related to the original function of pDC, i.e., immune response, especially losses of 6q23 (*IFNGR1*, *TNFAIP3)*, 9p21.3 (cluster of *IFNA* genes), and 12p13.2-p13.1 (*CLEC2B*, *CLEC4C*, *CLEC4E*, *TNFRSF1A)* [8]. Thus, those deletions compromise the normal function of the cells of origin of BPDCN.

2.2. Inactivation of Genes Encoding Cell-Cycle Inhibitors and Tumor Suppressor Genes

Similarly to other hematological malignancies, deletions inactivating Tumor Suppressor Genes (TSG), such as *TP53* [9][10][11][12], responsible for genetic instability, are also found in BPDCN. The tumor suppressor gene ATM, mutated in lymphoproliferative syndromes [13], may also be mutated in BPDCN [12], while *RB1*, involved in the regulation of the G1/S cell cycle transition, is also frequently deleted [5][10][12][14]. Initially described in retinoblastoma, in which it modeled the principle of TSG [15], *RB1* is also reported in chronic lymphocytic leukemia and Acute Lymphoblastic Leukemia (ALL) [16]. Additionally, the *CDKN1B/CDKN2B/CDKN2A* genes have a role in the G1/S transition, and their deletions are reported in some studies [2][5][10][12][17], similar to ALL [16] and lymphoma [18]. This alteration in cell cycle regulation could have a crucial role in the oncogenesis of BPDCN [10].

2.3. Recurrent Deletions in 5q31

Deletion in 5q are particularly recurrent in BPDCN, constituting a specific defect compared to other hematological malignancies [3][19]. In the 5q23.3 Common Deleted Region (CDR), *HINT1* was first proposed to be a key gene [19]. Indeed, *HINT1* encodes a homodimeric purine phosphoramidase, suggesting a transcriptional modulatory role. Moreover, *HINT1* deficiency would impair ATM function and thus DNA repair [19]. On the other hand, the 5q31 locus would also be a key region on chromosome 5, with deletions delineating a group of unfavorable prognostic impacts [3]. The glucocorticoid receptor gene *NR3C1* was found to be recurrently deleted, leading to haploinsufficiency and decreased glucocorticoid receptor activity [3]. The deletions impact the polycomb complex, in particular *EZH2*, with dysregulation of the *HOXA* locus and plasmacytoid dendritic differentiation.

2.4. Deletions of Transcription Factors

Similarly to other hematological neoplasms, transcription factor are particularly impacted in BPDCN. *ETV6* (*TEL*) is frequently mutated or deleted [1][5][8][9][10][17], contrasting with classical defects in other leukemia where translocations are more frequent, including t(12;21)(p13;q22) *ETV6::RUNX1* in B-cell Acute Lymphoblastic Leukemia (B-ALL) [20], t(5;12)(q32;p13) *ETV6::PDGFRB*, t(9;12)(p24;p13) *ETV6::JAK2* or t(4;12)(q12;p13) *ETV6::PDGFRA* in hypereosinophilic syndromes, and other translocations in rare cases of Acute Myeloid Leukemia (AML) [21]. ETV6 invalidations are, however, known in leukemia: somatic mutations of *ETV6* remain rare

in AML [21], but germline mutations are also possible in the context of thrombocytopenia predisposing to AML, Myelodysplastic Syndromes (MDS), Chronic MyeloMonocytic Leukemia (CMML), B-ALL, or multiple myeloma [22].

The IKAROS family (*IKZF1/2/3*) is also frequently deleted [2][9][14][23], similarly to ALL [24], where it compromises lymphoid differentiation [25]. *ZEB2* may also be altered in BPDCN [26]. This transcription factor is involved in the commitment and lineage fidelity of myeloid and lymphoid cells at various stages of hematopoiesis and is thought to play a key role in the development of various types of AML, ALL, and lymphoma [27].

While translocations involving transcription factors have been widely described in ALL and AML, recurrent rearrangements in BPDCN were rare before 2017. Indeed, *KMT2A* (*MLL*) rearrangements had previously been described in rare cases of CD4+ CD56+ neoplams identified as BPDCN (*KMT2A::ENL* and *KMT2A::MLLT1*) [28][29], but these descriptions in BDPCN have been challenged because these reported cases do not fulfill the current diagnostic criteria of BPDCN. Indeed, these cases could correspond to CD4+ CD56+ AML, because they constitute a delicate differential diagnosis for BPDCN [30].

2.5. Recurrent MYC Rearrangements

Initially, the translocation t(6;8)(p21;q24) was sporadically reported by several studies, using conventional karyotyping. Since 2018, *MYC* rearrangements (8q24) have been largely described in approximately 30% of BPDCN [23][31][32][33], with a more frequent immunoblastoid morphology and sometimes a CD56-negative phenotype [31][34].

These *MYC* abnormalities bring BPDCN closer to high-grade B lymphoma [2][6][31][35], but the gene partners are really different, with specific partners that could point towards pDC differentiation. Indeed, among *MYC* rearranged cases of BPDCN, Sakamoto et al. confirmed the high prevalence of the t(6;8)—detected in 56% of cases involving the *RUNX2* locus at 6p21. Interestingly, Kubota et al. showed that the t(6;8) juxtaposes the promoter of *MYC* to the pDCs-specific *RUNX2* super-enhancer, leading to overexpression of *MYC*. In this recurrent t(6;8)(p21;q24), both *MYC* and *RUNX2* are dysregulated, and cooperate together to promote survival and proliferation of the BPDCN cells. Remarkably, *RUNX2* is physiologically involved in differentiation and migration of pDCs and plays a dominant role in controlling transcription networks in BPDCN [36].

Other partners of *MYC* have been sporadically reported but not clearly identified (i.e., 2p12, Xq24, 3p25, 14q32). It remains to be determined if *MYC* rearrangement could constitute a primary or secondary genetic event in BPDCN. In this way, the t(6;8)(p21;q24) cannot be considered as a specific genetic abnormality of BPDCN because it has been reported in follicular lymphoma [37]. Lastly, a unique study showed the adverse impact of *MYC* rearrangement, and this prognostic impact still needs to be confirmed by further independent studies [31].

2.6. Recurrent MYB Rearrangements

In 2017, other recurrent rearrangements were described in nine of fourteen patients, including five children [14]. Remarkably, all five children included in this series had a *MYB* rearrangement. Of note, the previous largest report

of pediatric BPDCN cases exhibited several cases with 1q and/or 6q abnormalities, or translocation t(1;6)(q21;q23) [38]. These observations reveal a striking link between pediatric BPDCN and *MYB* rearrangement.

MYB rearrangements create fusion transcripts between *MYB* and various partner genes (*ZFAT*/8q24, *PLEKHO1*/1q21, *DCPS*/11q24, *miR-3134*/3p25) [14]. The chimeric transcripts retain the MYB transactivation domain and disrupt its negative regulatory domain, which allows the maintenance of the *MYB* transcriptional activity. Indeed, functional analysis of *MYB* fusions revealed the activation of *MYB* target genes as a result of induced *MYB* activation [14]. *MYB* is a nuclear-localized transcriptional activator in hematopoietic cells that interacts with the C/EBP complex to stimulate the transcriptional activity of *MYC*, *BCL2*, *c-KIT*, *c-ERBB2*, and other targets (**Figure 1**). Its expression progressively decreases during cell differentiation, with high activity in hematopoietic stem cells and activated T-cells.

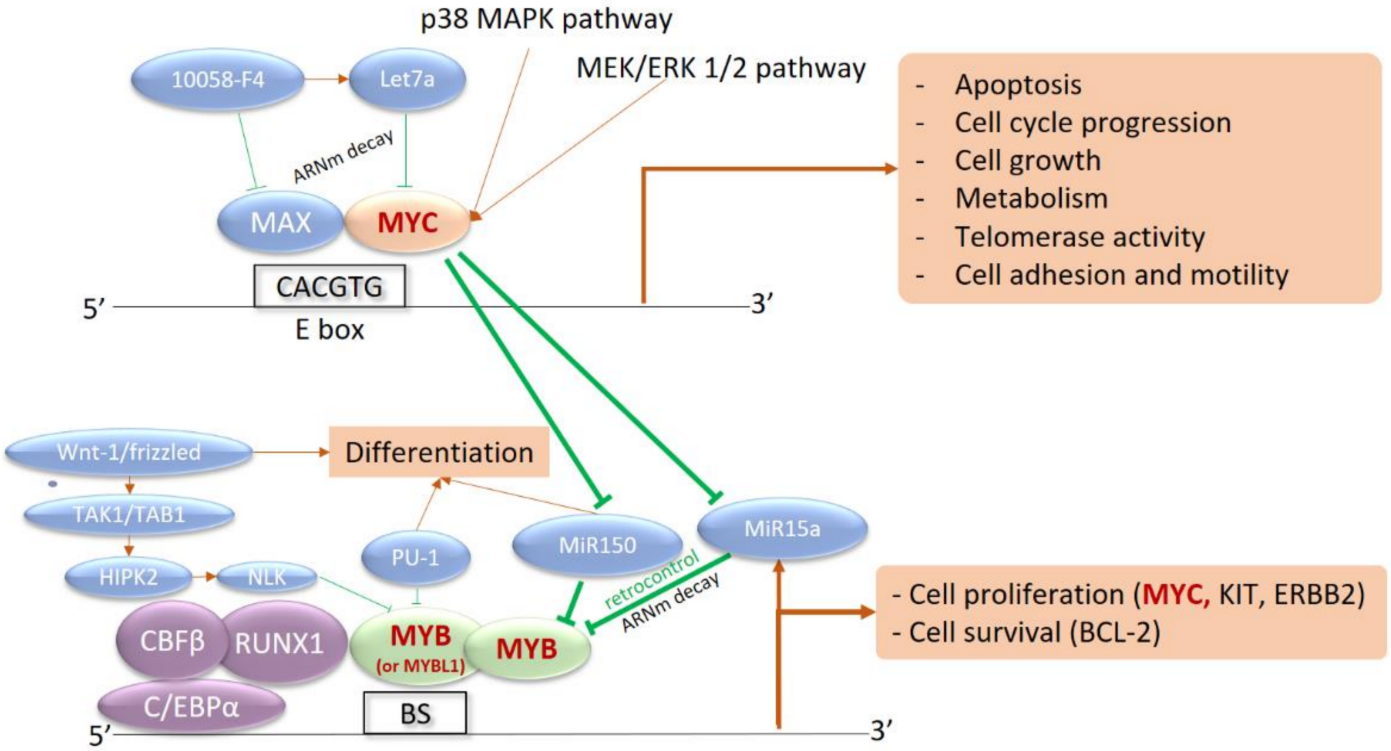

Figure 1. Interaction network between MYB, MYC, and their transcriptional targets. MYC is a strong transcriptional activator, dependent on the intracellular phosphorylation cascade signaling pathways of Mitogen-Activated Protein Kinases (MAPK) and Extracellular signal-Regulated Kinases (ERK) (p38 MAPK and MEK/ERK pathways 1 and 2). Activation of MYC induces the transcription of numerous target genes involved in proliferation, division, metabolism, and cell motility, as well as apoptosis. MYC also inhibits microRNAs (MiR150 and MiR15a) that are capable of silencing MYB expression in the basal state. Activation of MYC therefore induces activation of MYB, involved in the core binding factor (CBF) complex with CBFB, RUNX1, and CEBPA. MYB is also a transcriptional activator recognizing multiple nucleotide sequences, in a complex with CEBP. The targeted genes are involved in survival with BCL-2 and cell proliferation with c-KIT, c-ERBB2, and especially MYC. This results in an activation loop between the two transcriptional activators: BS, MYB Binding Site with MYB Recognition Element.

In contrast to *MYC*, *MYB* is only exceptionally rearranged in other hematological malignancies: in fact, only in rare cases of acute basophilic leukemia with *MYB::GATA1* fusion transcripts, even rarer than BPDCN [39] and in T-ALL with t(6;7) and *MYB* duplication [40]. *MYB* translocations are also reported in 60–80% of adenoid cystic carcinomas, mainly with the *MYB::NFIB* fusion transcript [41][42], and in pediatric gliomas [43]. For the first time, fusion transcripts appear to be recurrent and specific for BPDCN compared to other hematological malignancies. *MYB* may play a key role in the leukemic transformation process, similar to *MYB::GATA1* rearrangements in acute basophilic leukemia. However, the frequency of *MYB* rearrangements is very uncertain and possibly higher in young patients, as suggested by the original study [14].

Interestingly, an analog of *MYB*, *MYBL1* would also be rearranged in a very similar way, with an identical functional impact [31]. Finally, *MYB*, *MYBL1*, and *MYC* defects would be mutually exclusive, delineating distinct groups of patients [31].

2.7. Mutation Landscape

2.7.1. A Myeloid-like Profile

In addition to these cytogenetic defects, the mutation landscape of BPDCN has been particularly studied. However, given the rarity of BPDCN, only small cohorts have been studied so far (less than 30 cases), and usually by targeted high-throughput sequencing. Nevertheless, 22 Whole Exome Sequencing (WES) have been performed [7][9][44]. On a first stratum, the mutation landscape is quite similar to myeloid neoplasms [45][46][47][48][49][50], with a high prevalence of mutations involving epigenetics (*TET2*, *ASXL1*) and splicing (*ZRSR2*, *SRSF2*, *U2AF1*) [9][11][51][52][53]. These mutations rather suggest an early process before leukemic transformation, as is well described in AML, disturbing the DNA methylation balance, modifying chromatin access and the splicing processes [54]. In multistage leukemogenesis models, epigenetics and splicing mutations would be present from the pre-leukemic stages [55], and their frequency increases with age. Of note, mutations of *TET2* are found in 40 to 60% of cases [9][11][53]. Interestingly, loss-of-function of ZRSR2 impairs pDC activation and apoptosis after inflammatory stimuli with intron retention, promoting pDC expansion. Of note, being located on the X chromosome, this enrichment of ZRSR2 in BPDCN fits well with its predominance in males [52]. Although mutations of *NPM1* were initially described in BPDCN [9], this has not been confirmed since, and this is not consistent with the nature of these mutations defining a mutually exclusive subtype of AML [22]. In contrast, sub-clonal mutations of signaling pathways can be found in 5 to 20% of BPDCN, especially *FLT3*, *KIT*, *KRAS*, and *NRAS* mutations [9][12][14][26][44][45][53][56][57][58]. This profile is close to that of CMML and is consistent with a common clonal origin of BPDCN and CMML cells demonstrated in a few patients suffering from the two neoplasms [7][45]. The leukemic model would include shared epigenetic mutations, with secondary emergence of a BPDCN clone and another clone leading to CMML [48][59] or AML [60][61][62][63].

2.7.2. Some Lymphoid-like Features

Associated with these “myeloid-like”, key deleted transcription factors or tumor suppressor genes *IKZF1*, *ETV6*, *RB1*, *ATM,* and *TP53* can also be mutated in some cases (5–10%), also resulting in an

invalidation [2][4][6][7][11][64][65]. Notably, biallelic invalidations of *ETV6* argue for a primordial early event, possibly overexpressing the BPDCN oncogene *TCL1A* [4][8][66]. *IKZF1* loss-of-function, either by deletion or mutation, would lead to the increased cell interactions in BPDCN. BPDCN also exhibit *KMT2D* and *SYNE1* mutations or losses, previously reported in follicular lymphoma [6][64]. Overall, the most characteristic feature of BPDCN would be that combination of myeloid-like and lymphoid-like abnormalities (**Figure 2**).

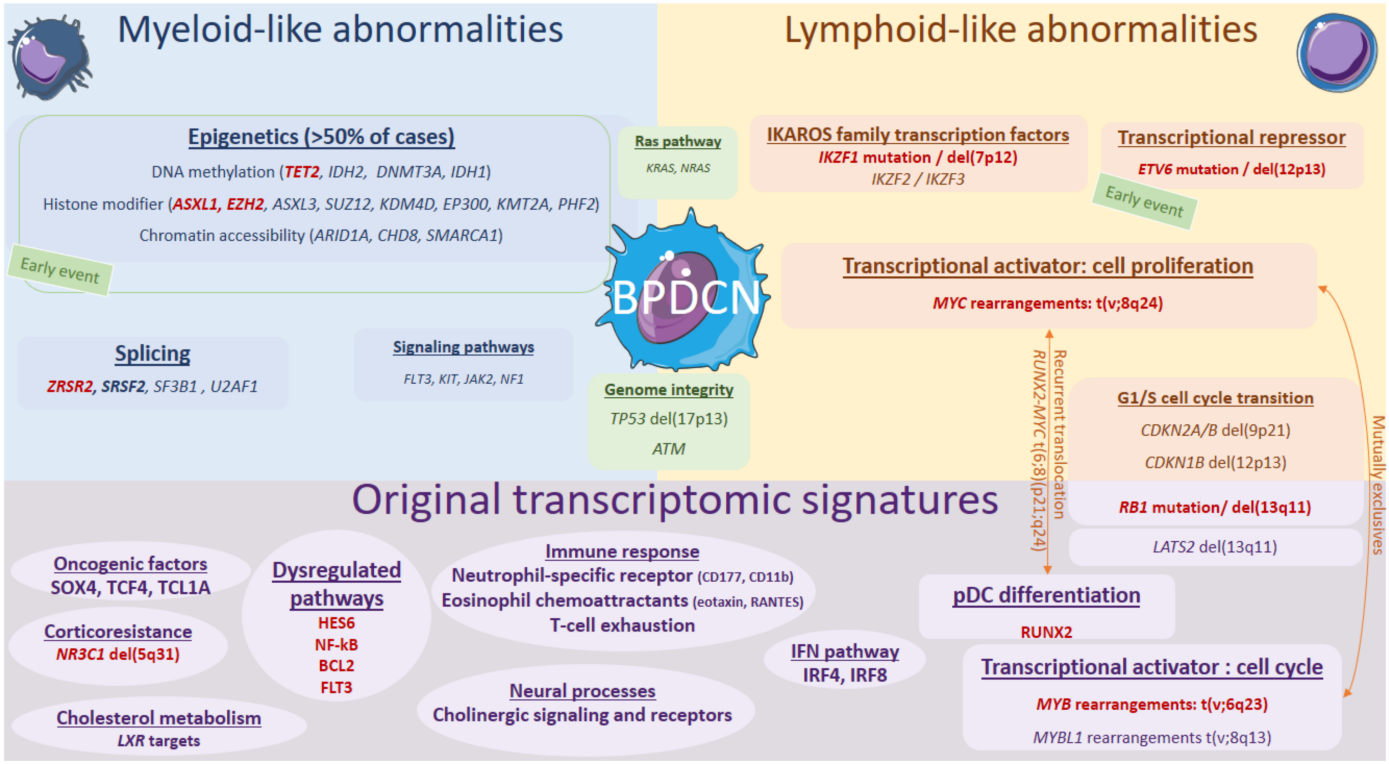

Figure 2. Genomics and transcriptional landscape of BPDCN. The genomic landscape of BPDCN include a combination of myeloid-like and lymphoid-like mutations and cytogenetic defects within a complex landscape, with frequent complex karyotypes. The transcriptional program of BPDCN is made of a diversity of original factors: RUNX2, MYB, IFN pathway, neural processes, cholesterol metabolism, corticoresistance factor, and original oncogenic factors.

2.8. Prognostic Factors

A major challenge to determine the mutation landscape in BPDCN is to establish a molecular prognostic stratification, as in AML with the *European Leukemia Network* recommendation [67]. Nevertheless, this point remains a tricky issue because of the rarity and diagnostic challenges of BPDCN. Some adverse prognostic factors have still been proposed, particularly mutations involving *ETV6*, *TP53*, or *NRAS/KRAS* [9], as well as biallelic deletions of 9p21.3 [1][2], deletions of *NR3C1* [3], abnormal karyotype or numerous abnormalities detected [68][69], and rearrangements of *MYC* [31][70]. At this time, it is unfortunately impossible to integrate all of these factors into a score stratifying patients, and most of these prognostic abnormalities need to be confirmed.

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