

Review Article

Extranodal NK/T-Cell Lymphoma: Toward the Identification of Clinical Molecular Targets

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Extranodal natural killer (NK)/T-cell lymphoma of nasal type (NKTCL) is a malignant disorder of cytotoxic lymphocytes of NK or more rarely T cells associated with clonal Epstein-Barr virus infection. Extranodal NKTCL is rare in Western countries, but in Asia and Central and South America it can account for up to 10% of non-Hodgkin's lymphomas. It is an aggressive neoplasm with very poor prognosis. Although the pathogenesis of extranodal NKTCL remains poorly understood, some insights have been gained in the recent years, especially from genome-wide studies. Based on our own experience and knowledge of the literature, we here review some of the genomic and functional pathway alterations observed in NKTCL that could provide a rationale for the development of innovative therapeutic strategies.

1. Introduction

The term extranodal natural killer/T-cell lymphoma (NKTCL) refers to a group of clonal proliferations of cytotoxic lymphocytes of natural killer (NK) or, more rarely, T-cell types, with peculiar clinicopathologic features, arising mainly as tumors or destructive lesions in the nasal cavity, maxillary sinuses, or palate [1]. More rarely, extranodal NKTCL may present in other extranodal sites such as skin, testis, lung, or gastrointestinal tract and tend to have a more adverse clinical outcome [2–4]. This is particularly true when one defines nonnasal cases as extra upper aerodigestive tract cases as in the study of Lee et al. which reports survival rates of 20% versus 54% for the patients with nasal and upper airway region localizations [4]. However, as noted by several authors, many nonnasal NKTCL might

represent disseminated nasal NKTCL, knowing that such dissemination can occur early in the clinical course of the disease and toward sites that are localizations where nasal NKTCL will metastasize to. Besides the more adverse clinical features, for which the underlying mechanisms need to be defined, there are no significant differences in age, gender, ethnicity, bone marrow involvement, hemophagocytosis, or immunophenotypic profiles between nasal and nonnasal NKTCL. Very rare cases with primary lymph node involvement have also been described [5]. Extranodal NKTCL shows a wide cytological spectrum and is characterized by frequent features of angioinvasion and angiocentrism, which often result in coagulative necrosis. Typically, tumor cells express cytoplasmic CD3 ϵ , CD2, CD56, lack CD5, CD4, and CD8, and have an activated cytotoxic immunophenotype with expression of perforin,

granzyme B, and TiA1. The cell of origin of these tumors has been debated. Indeed, the identification of CD3 expression in tumor cells in necrotic lesions has led to the terminology of angiocentric T-cell lymphoma [6–8] adapted in the REAL classification [9], before it was demonstrated that tumor cells express several chains of the CD3 complex in the cytoplasm, but lack T-cell receptors (TCR) and have TCR genes in a germline configuration, consistent with an NK-cell origin [10, 11]. If the majority of NKTCL are likely to originate from mature NK cells, a small proportion of cases, with expression of $\gamma\delta$ or $\alpha\beta$ TCR appear to derive from cytotoxic T lymphocytes, reflected in the “NK/T” cell terminology.

Extranodal NKTCL represents the major group of mature NK cell neoplasms in the recently revised WHO classification of hematolymphoid tumors, which also include the aggressive NK cell leukemia (ANKL) and a provisional group of chronic NK-cell lymphoproliferative disorder of uncertain malignant potential, most likely related to T-cell large granular lymphomas [1]. Importantly, both NKTCL and ANKL are Epstein-Barr virus- (EBV-) associated neoplasms as the virus is found in their tumor cells [12, 13]. Although the precise role of the virus in the etiology of the disease is poorly understood, the study of EBV gene polymorphism has shown that tumor cells are clonally infected as opposed to normal nasal tissues [14, 15]. Circulating EBV viral load is an important prognostic factor, and plasma EBV DNA levels can also be used for disease monitoring [16]. In this respect, the incidence of NKTCL parallels the geographic distribution of EBV infection with prevalence in the Asian and Central and South American populations, where it can account for up to 10% of non-Hodgkin's lymphomas [17–19].

Despite a localized presentation in most patients, extranodal NKTCL is an aggressive disease with poor prognosis. The 5-year survival rate is less than 50%. In the absence of effective treatment, the median survival for advanced-stage disease is only 6–12 months [19–22]. The retrospective International Peripheral T-cell Lymphoma project recently reported a median overall survival of 7.8 months for NKTCL, corresponding to the poorest survival among all T-cell lymphoma entities [2]. Therefore, despite progress with combined field radiotherapy and chemotherapy, autologous bone marrow transplantation and the promising effect of L-asparaginase treatment in relapsed cases [16, 23], NKTCL remains difficult to cure, and the need for alternative therapeutic strategies has prompted researchers to explore oncogenic pathways involved, to provide new molecular targets. This review will focus on these potential molecular pathways that have been implicated in the physiopathology of NKTCL, in particular through the lights shed by several recently reported genome-wide profiling studies [24–30].

2. EBV Infection and Viral Protein Expression

Several lines of evidence point at EBV as a major player in the pathogenesis of NKTCL. First of all, when dealing with an EBV-associated malignancy, one can think of NKTCL as a potentially highly immunogenic lymphoma that could benefit from cellular immunotherapies targeting the viral antigens

as in posttransplant B-cell lymphoproliferative disorders [31]. These B-cell proliferations, like the *in vitro* infected B-cell-derived lymphoblastoid cell line (LCL), express the full spectrum of EBV latent proteins (latency III). The latent phase consists of the maintenance of the EBV genome as a circular episome that is replicated by the cellular DNA polymerase. Latent type III infection is associated with the expression of six EBV-encoded nuclear antigens (EBNA): EBNA1, EBNA2, EBNA2A, EBNA3B, EBNA3C, and EBNA leader protein (EBNA-LP); three cell surface proteins: latent membrane protein (LMP) 1, LMP2A, and LMP2B; two EBV-encoded RNAs: EBER1 and EBER2. Among these proteins, the EBNA3s are believed to be particularly immunogenic for the generation of specific cytotoxic T lymphocytes (CTL). However, similarly to Hodgkin's lymphoma, NKTCL is believed to be in latency II, with a more restricted pattern of viral proteins expressed, limited to EBNA1, LMP1, and LMP2 [32]. EBNA1 is required for the maintenance of viral episomes and expressed in all latency phases. LMP1 is the main transforming protein of EBV. It is essential for EBV-induced B-cell transformation *in vitro*, acting like a constitutively activated tumor necrosis factor receptor family member, activating NF- κ B pathway and promoting cell survival. LMP2A and LMP2B are generated by alternative splicing and, although not essential for B-cell transformation, can also promote proliferation and survival. However, LMP2 has only been demonstrated at the transcriptional level in NKTCL. LMP1 expression is also variable, and when expressed it is often limited to a subpopulation of tumor cells, possibly under the pressure of host immune surveillance. Despite these challenging conditions, attempts have been made to generate *in vitro* LMP2-specific CTL using antigen-presenting cells overexpressing LMP2, to treat Hodgkin's lymphoma and NKTCL patients [33]. The cytotoxic activity of these LMP2-specific CTL have been confirmed against NKTCL-derived cell line, which led to the discovery of a unique alternative transcript of LMP2 (LMP2-TR) that uses a new promoter located in the terminal repeat region of the episomal EBV, not expressed in B-LCL [34]. LMP2-TR may constitute a promising target for adoptive cellular immunotherapy in NKTCL.

EBV is a B-lymphotropic virus, infecting B cells through interaction with its cellular receptor CD21, and establishing a lifelong infection in more than 90% of the human adult population. Although the precise mechanism involved in NK- or T-cell infection is unknown, passive acquisition of CD21 in the NK/T-cells by membrane fragment exchange during cytotoxic interaction, a process known as trogocytosis, has been proposed [35, 36]. Chronic active EBV infection (CAEBV) was first recognized as severe illness related to chronic or persistent EBV infection [37, 38]. CAEBV is a life-threatening disease characterized by infectious mononucleosis-like symptoms with virus-associated hemophagocytic syndrome. Like in NKTCL, clonal proliferations of EBV-infected NK- or T-cells are seen in patients with CAEBV, making this disease more likely a chronic lymphoproliferative disorder or a premalignant stage as some CAEBV patients can actually develop subsequent NKTCL [39]. Whether the EBV-host interaction may play a role

in the development of NKTCL is still a pending question. Performing comparison of EBV and cellular gene expression profiling in NKTCL- and CAEBV-derived cell lines, Zhang et al. reported the transcription of lytic phase genes such as *BZLF1*, *BARF1*, *BFLF2*, and *BDLF3*, despite the absence of virion DNA production and cellular gene signature implicating mainly cell cycle and apoptosis-related genes such as *TNFRSF10D*, *CDK2*, *Hsp90*, *IL12A*, and *PDCD4* [30]. Beside the expression of latency II genes, expression in NK/T-cell lines, of lytic phase genes (such as *BZLF1*) capable to interact with multiple cell cycle control proteins is intriguing. EBV may exert oncogenic effects through the production of cytokines such as Interleukin 9 (IL-9) [26] and IL-10 [40]. EBV-induced production of IP10/MIP2 chemokines may contribute to vascular damage and necrosis [41]. Obviously, the way viral gene products interact with cellular host metabolism needs to be clarified and may lead to novel targets for therapies.

3. NK Cell Antigens and Cytotoxic Activity

Irrespective of their NK, $\alpha\beta$ -, or $\gamma\delta$ -T-cell lineage, NKTCL is a lymphoma of activated cytotoxic lymphocytes as evidenced by the expression of cytotoxic molecules such as perforin, granzyme B, and TIA1 [42]. Whereas T cells use their TCR for antigen recognition and control of their specific cytotoxic activity, NK cells use MHC class I-specific NK cell receptors (NKR) for this purpose [43]. NK cells are part of the innate immune system involved in the immunosurveillance [44]. Engagement of inhibitory NKR by self-MHC class I on potential target cells inhibits cytotoxicity whereas loss of MHC class I expression due to transformation or viral infection, results in a loss of this inhibition. There are two types of NKR: the killer immunoglobulin-like receptors (KIR) and the killer cell lectin-like receptors (KLR or CD94/NKG2 complexes). KLR as well as other NK cell markers like CD56 can also be expressed by $\alpha\beta$ - or $\gamma\delta$ -cytotoxic T cells. The *KIR* locus located on human chromosome 19, exhibits a substantial haplotypic and allelic diversity [45, 46]. The KIR haplotypes have been separated into two groups, containing from 7 to 12 genes [47]. The expression of KIR at the cell surface is clonally distributed, meaning that a clonal NK/T-cell population is expected to express a restricted KIR repertoire as shown in NKTCL [48–50]. Another example of the interest of KIR in malignant lymphomas is given by KIR3DL2 that proved to be a valuable tool in the diagnosis, and perhaps a clinical target, of Sézary syndrome, a cutaneous CD4⁺ T-cell lymphoma with systemic dissemination [51–53]. KLR are C-type lectin receptors that precede the expression of KIR during NK cell development. They consist of molecules of the NKG2 family such as NKG2A (KLRC1), NKG2C (KLRC2), or NKG2E (KLRC3), form heterodimer with earlier expressed CD94 at the surface of maturing NK cells [54]. In addition to immature NK cells, a subset of mature NK cells also lack CD94/NKG2 expression as a consequence of the clonal diversification phenomenon. Interestingly, expression of CD94 has been associated with a better prognosis in NKTCL [55]. Although NK activity was

identified from the initial description of ANKL [56, 57], the cytotoxic activity of the NKTCL tumor cells has not been particularly investigated due to the difficulty to isolate these cells.

4. Survival/Apoptosis

The mechanisms by which NKTCL cells survive and escape immune surveillance are unknown. One way for an NKTCL tumor cell to escape anti-EBV immunity is to lower its expression of EBV antigens, particularly LMPs proteins. It is also known that cytotoxic effector cells have a proper way to resist to their own cytotoxic agents [58]. The main cytotoxic pathway used by NK and CTL involves the release from specialized granules of cytotoxic molecules including perforin and granzymes, triggering a process leading to DNA fragmentation and apoptosis. In particular, granzyme B (GZMB), by activating directly or indirectly caspase-3, leads to rapid execution of apoptosis. SERPINB9 (also known as PI9) is a GZMB-specific serine protease inhibitor that can protect effector cells from their own cytotoxic activity. It has been shown that SERPINB9 can make hepatocytes resistant to lysis by CTL or NK cells [59] and may participate to the mechanism for tumor escape in NKTCL [60]. Interestingly, its loss of expression was described as a poor prognostic factor in a study of 48 NKTCL patients [20].

Although it seems that tumor cells are resistant to the killing via GZMB, NKTCL are frequently associated with zonal tumor cell death, tissue necrosis, and vascular damage. The production of chemokines like CXCL9 (Mig) and CXCL10 (IP10), in response to interferon γ released by activated tumor cells, may contribute to the observed damages [41, 61]. Although Fas (CD95) as well as Fas ligand (FASL/CD95L) are frequently well expressed in NKTCL cells, mutations of the *FAS* gene are observed in 50 to 60% of cases, most likely contributing to resistance to apoptosis [62]. Indeed, most of the *FAS* gene mutations are frameshift mutations arising in the death domain, leading to mutated proteins on the cell surface, unable to transduce the apoptotic signal [63]. High expression of FASL is also a way for tumor cells to evade immune response by deleting Fas-expressing infiltrating T cells. In line with these observations, NKTCL has long been known as resistant to combination chemotherapy. This resistance is also complicated by the high expression of p-glycoprotein, encoded by multidrug resistance gene 1 (*MDR1*) that acts as an energy-dependent efflux pump for various drugs [64].

Very recently, survivin (BIRC5), an inhibitor of apoptosis frequently involved in tumor oncogenesis, was found overexpressed in NKTCL [28]. The authors proposed that survivin could be a useful therapeutic target in NKTCL. In *in vitro* studies, they showed that Terameprocol, a survivin inhibitor, could downregulate survivin expression and induced apoptosis in NK cell lines.

5. Cytogenetic Analysis

Lymphomas arise from clonal expansion of transformed lymphoid cells through the accumulation of genetic lesions.

Currently, no genetic abnormalities specific for NKTCL have been identified. Cytogenetic analyses of NKTCL are difficult because of necrosis, small-size samples, and contamination by inflammatory reactive cells. Despite these difficulties, several studies using comparative genomic hybridization (CGH) and loss of heterozygosity (LOH) techniques have been reported [65–70]. Altogether, these studies identified gains at chromosomes 1p, 6p, 11q, 12q, 17q, 20q, Xp, and losses at 6q, 11q 13q, and 17p. In particular, the most frequent deletion was observed at 6q21–25 in all but one study. Sun et al. tried to define a minimal tumor suppressor gene-containing region involved in del6q25 and identified a 2.6 Mb interval located between *TIAM2* and *SNX9* genes [69]. More recently, progress in the DNA chip technology allowed the development of genome-wide array-based CGH (aCGH) giving access to better resolutions. The first report, from Nakashima et al., performed with homemade arrays with 1.35 Mb resolution, studied 10 of ANKL and 17 NKTCL cases and reported differences in their genomic alteration patterns (see Table 1) [27]. Loss of 7p (40%) and 17p13.1 (40%) and gain of 1q (43%) occurred more frequently in ANKL whereas loss of 6q did not. On the other hand, loss of 6q21–q22.1 (35%), 6q22.33–q23.2 (47%), 6q25.3 (29%), and 6q26–q27 (35%) were more frequent in NKTCL. Other alterations in NKTCL compared to ANKL include gain in 2q and loss of 1p36.23–p36.33, 2p16.1–p16.3, 4q12, 4q31.3–q32.1, 5p14.1–p14.3, 5q34–q35.3, and 11q22.3–q23.3. Two recent studies extended these findings by comparing submegabase resolution aCGH and gene expression profiling on NK cell lines as well as NKTCL tumor samples [24, 71]. These two studies emphasize recurrent genomic abnormalities observed in about half of the patients: gain of 1q21–q44, and losses of 17p11.2–p13.3 and 6q21. In particular, this region of del6q21 contains four candidate tumor suppressor genes, *PRDM1*, *ATG5*, *AIM1*, and *HACE1*, which decreased expression was confirmed at the RNA level. In their study, Iqbal et al. found mutations and methylation in *PRDM1*, *ATG5*, and *AIM1* in NKTCL cell lines [71]. *ATG5* is part of the autophagy pathway implicated both in apoptosis and in the maintenance of energy homeostasis during starvation [72]. The role of autophagy in oncogenesis is, however, the object of controversy [73]. *AIM1* which stands for “absent in melanoma-1” is still poorly characterized but was reported as a good tumor suppressor gene candidate in malignant melanoma, exerting its effects through interactions with the cytoskeleton [74]. *PRDM1* is a transcriptional regulator, initially described as a suppressor of beta-interferon gene expression, that is associated with the terminal differentiation of B lymphocytes and T-cell homeostasis and function [75, 76]. It was found mutated in some diffuse large B-cell lymphomas, and it was concluded that its inactivation contributes to lymphomagenesis by blocking differentiation of postgerminal center B cells to plasma cells [77]. Loss-of-function due to mutations as well as transcriptional inhibition by DNA methylation observed in NK cell lines, suggest a tumor suppressor role of *PRDM1* in NKTCL [71].

HACE1 is another candidate tumor suppressor gene [24, 90]. Characterization of the chromosome 6q21 breakpoint,

frequently involved in sporadic Wilm’s tumors, led to the identification of the *HACE1* gene [91]. It encodes a member of the HECT family of E3 ubiquitin ligases that tag specific target proteins to degradation by the proteasome or to control their subcellular localization [85]. Because of their involvement in controlling crucial signaling pathways, E3 ubiquitin ligases appear as important regulators of cancer development and therapy. It is downregulated in multiple human cancers and maps to a prominent tumor-suppressor region of LOH in many tumors including lymphomas. *HACE1*^{-/-} mice are also prone to spontaneous development of various types of cancers [90]. Our integrated genomic and transcriptomic analysis of NKTCL tumor samples and cell lines has shown downexpression of *HACE1* gene irrespective of the presence of del6q21 alteration [24]. In addition, we could show by methylation-specific PCR and product sequencing (data not shown) that hypermethylation of CpG-177 island located directly upstream of *HACE1* locus, is responsible of the silencing of the diploid gene or the remaining allele. Although the mechanism of antitumor action of *HACE1* is still unclear, it has been shown that overexpression of *HACE1* in the 293T cell line inhibits cell proliferation via the degradation of phosphorylated cyclin D1 [90]. This suggests a possible mechanism for *HACE1* to regulate cell cycle exit by reducing cyclin D1 levels. Existence of other *HACE1* targets is possible as suggested by the recent identification of retinoic acid receptor beta 3 as an *HACE1* interacting protein [92].

6. Cell Signaling Pathways

Although the anomaly of signaling pathways involved in the pathogenesis of NKTCL is not deciphered, progress has been made in the recent years that will help to define candidate therapeutic targets.

6.1. Jak-Stat Pathways. Signal transducers and activators of transcription, STATs, are transcription factors activated in response to cytokines or growth factors [80]. The activation of STAT signaling pathways requires tyrosine phosphorylation of the STAT proteins that results from their association with growth factor receptors having intrinsic tyrosine kinase activity, or through recruitment of members of the Janus kinase (JAK) family to activated surface receptors. A direct link between STAT signaling and oncogenesis was established when it was shown that constitutive STAT activation by oncogenic tyrosine kinases from *Src* or *Abl* families, directly participates to cell transformation [93, 94]. Accordingly, a large number of tumors, both in primary cells as well as in tumor-derived cell lines, display constitutive activation of STAT factors. In particular, STAT3 role in oncogenesis is well documented in anaplastic large cell lymphoma where STAT3 activation was shown to provide growth advantage and resistance to apoptosis of ALK⁺ tumor cells [81, 95, 96]. In NKTCL, STAT3 was found constitutively activated, by phosphorylation on Y705, and localized in the nucleus in 90% of the patients studied [24, 82]. Inhibition of endogenous

TABLE 1: Recurrent genomic alterations in extranodal NKTCL from published data.

Chromosomal location	Frequency (%)						
	Huang et al. 2010 [24]	Iqbal et al. 2009 [71]	Nakashim et al. 2005 [27]	Yoon and Ko 2003 [70]	Ko et al. 2001 [66]	Siu et al. 2000 [67]	Siu et al. 1999 [68]
<i>Gains</i>							
1q21–q44	50	50	50				20
2q13–q14		26	24		29		
2q31.1–q32.2		20	24		43		
6p25–p11.1	40	25	40				
7q11.2–q34	50	32	24				20
7q35–q36	60	40					40
17q21.1	20	50			29		40
20pter–qter	30	45					50
<i>Losses</i>							
6q16–q25	40	50	38	80		49	25
11q23.1	30	13	29			31	20
11q24–q25	40	25					20
13q14.11	30	27	25			14	60
17p13.3	40	45	40		43	40	20

TABLE 2: Potential Therapeutic targets for extranodal NKTCL.

Pathways	Genes	Expression	Chromosomal location	References
EBV	LMP2-TR	Up	N.A.	[32]
<i>Survival/apoptosis</i>				
	CCND3	Down	6p21.1	[69]
	SERPINB9	Down	6p25	[19, 57]
	FASL	Up	1q23	[60, 78]
	TNFAIP3	Down	6q23	[69, 79]
<i>Cell signaling pathways</i>				
JAK-STAT	STAT3	Up	17q21	[80, 81]
	JAK2	Up	9p24	[69, 81]
	IL10	Up	1q31–q32	[81, 82]
AKT	AKT1/2/3	Up	14q32.3/19q13.1/1q44	[69, 70]
NOTCH	NOTCH1	Up	9q34.3	[24, 83]
WNT	β -CATENIN	Up	3p22–p21.3	[24, 69]
PDGF	PDGFRA	Up	4q11–q13	[69]
	PDGFA/B	Up	7p22/22q12.3–q13.1	[69]
<i>Angiogenesis</i>				
	HGFR (MET)	Up	7q31	[78]
	VEGFR2	Up	4q12	[24, 69]
	VEGFA	Up	6q12	[24, 69]
	HIF1 α	Up	14q21–q24	[24, 70, 84]
<i>Tumor suppressor genes</i>				
del6q21	PRDM1	Down	6q21–q22.1	[70]
	ATG5	Down	6q21	[70]
	AIM1	Down	6q21	[70]
	HACE1	Down	6q21	[69, 85]
<i>Other pathways/genes</i>				
	TP53	Down	17p13.1	[86, 87]
	TP73	Down	1p36.3	[88]
	AURKA	Up	20q13	[24, 89]

N.A.: not applicable

activated STAT3 in NKTCL-derived cell lines, using transducible dominant-negative STAT3, leads to growth arrest and apoptosis inhibition [82]. These results are consistent with the known targets of STAT3 transcriptional activities that include survivin, cyclin D1, BCL-X_L, cMYC, vascular growth factor (VEGF), IL-10, and IL-6 [97]. Importantly, STAT3 activation promotes the production of immunosuppressive factors not only by the tumor cells but also by cells of the microenvironment through mediators such as VEGF or IL-10, activating STAT3 in these bystander cells that in turn restrains antitumor immune response [84, 98]. Targeting STAT3 and/or JAK2 for cancer immunotherapy may therefore be promising.

6.2. Angiogenesis Pathway. NKTCL is characterized by angiogenic growth and vascular damages with invasion of vessel walls by lymphoma cells. In this context, a search for genes associated with angiogenesis seems essential. The recent gene expression profiling studies have recorded overexpression of genes related to angiogenesis in NKTCL as compared to other peripheral T cell lymphomas or normal NK cells [24, 25]. Among those, one finds *VEGFA* an important downstream product of STAT3, and its receptor *VEGFR2* (*KDR*), both genes are upregulated, a finding confirmed by the immunohistochemical detection of VEGF α and its receptor in tumor cells. As mentioned previously, the production of VEGF by tumor cells not only may be used for autocrine growth and survival but also to maintain an immunosuppressive microenvironment by activating the STAT3 pathway. Vascular destruction observed in nasal type NKTCL results in hypoxia and the transcription activation of HIF α (hypoxia-inducible factor 1), a transcriptional activator that stimulates the expression of a number of genes implicated in angiogenesis (including *VEGFA* and *VEGFR2*) and in oxygen homeostasis [78]. Also observed is the upregulation of another important gene in angiogenesis, the *c-MET* proto-oncogene that encodes the tyrosine kinase cell surface receptor for the hepatocyte growth factor (HGF). HGF is a pleiotropic cytokine acting as an antiapoptotic, a promigratory, and a proliferating factor for a number of tissues. Interestingly, MET may be implicated in the prevention of FAS-mediated apoptosis of the FAS-expressing NKTCL tumors cells. This relies on the YLGA aminoacid motif located near the N-terminal region of MET that specifically binds to the extracellular portion of FAS and acts as a FASL antagonist and inhibitor of FAS trimerization [99].

6.3. PDGFR Pathway. The platelet-derived growth factor receptor- (PDGFR-) signaling pathway was also found activated in NKTCL cells [24]. The overexpression of PDGFRA mRNA in NKTCL compared to normal NK cells in microarray data is confirmed by the expression of PDGFR α and its phosphorylated form in primary tumors, shown by immunohistochemistry. Neither genomic abnormalities in the *PDGFRA* locus in 4q11–q13 nor mutations in the coding sequence or anomalies in the promoter region could be evidenced. The mechanism responsible for the activation of the PDGFR remains therefore unclear, but

like in PTCL NOS (PTCL not otherwise specified) [83], an autocrine feedback loop may explain the presence of the phosphorylated PDGFR α observed in all the 13 NKTCL cases examined. The potential of PDGF signaling pathway in NKTCL cell proliferation is illustrated by the dramatic dose-dependent inhibition of MEC04 cell growth observed in cultures performed the presence of imatinib mesylate [24].

6.4. Other Signaling Pathways. Pathways enriched in the gene signature of NKTCL include those of the NOTCH, WNT, and NF κ B signaling pathways [24, 25, 30]. However, and particularly in this tumor where necrosis is associated with strong infiltration of mesenchymal and lymphoid cells, it is sometimes difficult to attribute the differentially expressed genes to the tumor cells rather than to the microenvironment cells. In addition, differential expression needs confirmation in terms of biochemical activation. In particular, activation of the WNT pathway, comprising genes involved during the development and in oncogenesis, can be evidenced by the nuclear translocation of β -catenin. However, no nuclear expression of β -catenin could be observed in the neoplastic cells in our study by Huang et al. [24], making the targeting of WNT pathway of poor interest for therapeutic purpose. On the other hand, activation of the NOTCH pathway has been validated by Iqbal et al. [25]. NOTCH signals regulate development and differentiation of adult self-renewing cells, including T cells. Gamma-secretase is a critical component of the NOTCH signal transduction pathway [100]. Showing that inhibitors of γ -secretase can block the proliferation and survival of NK cell lines *in vitro*, was used for validation of NOTCH implication. Interestingly, *PTEN* is a tumor suppressor gene encoding a lipid phosphatase that antagonizes the activation of the PI3K/AKT pathway. NOTCH1 controls a transcriptional network that leads to activation of PI3K/AKT signaling and downmodulation of PTEN expression. NOTCH signaling and PI3K/AKT pathway act synergistically to maintain oncogenic activity in T-cell acute lymphoblastic leukemia [101]. PI3K/AKT was found activated in microarray analysis of NKTCL, and nuclear expression of phosphorylated-AKT was found in the nucleus of most NKTCL samples. NF κ B is a master regulator that controls the expression of a number of genes. Because EBV is known to activate NF κ B through LMP-1 and/or TRAF signaling [79], upregulation of NF κ B pathway in NKTCL versus normal NK cells is not unexpected. Signaling by the transcription factor NF κ B involves its release from its inhibitor I κ B, followed by its translocation into the nucleus. Nuclear detection by immunohistochemistry of RelA, the protein constituting the most abundant form of NF κ B, further supports the activation of this pathway in NKTCL. Interestingly, the tumor necrosis factor- α -induced protein gene, *TNFAIP3*, an inhibitor of NF κ B activity, was also found downregulated in NKTCL. This gene is located in 6q23, the region of recurrent loss discussed above, and loss of function of TNFAIP3 have also been reported in Hodgkin's lymphoma and other B-cell lymphomas [86, 102]. Surprisingly, the NF κ B pathway genes were not enriched in the NKTCL gene signature in the recent study of Iqbal et al. [25]. Questions

remain, therefore, to clarify the value of this pathway to identify therapeutic targets for NKTCL.

7. Other Pathways and Candidate Target Genes

Many other genes are found differentially expressed or targets for mutations or methylations in NKTCL when compared to normal NK cells (see Table 2). The list includes a number of oncogenes or tumor suppressor genes associated with many other tumors. *TP53* is a well-known tumor suppressor gene that causes cells with damaged DNA to arrest at G1 phase of the cell cycle. *TP53* is mutated in many cancers, and the frequency of NKTCL-mutated cases varies from 20 to 60%. *TP53* mutated cases have been associated with more advanced cases, suggesting that *TP53* mutation represents a secondary oncogenic event rather than a triggering mechanism for the development of NKTCL [87]. Nevertheless, *TP53* is found underexpressed in NKTCL transcriptomic analyses, and the observation that EBNA1 promotes *TP53* degradation [88] has to be considered to make *TP53* pathway a possible target for NKTCL therapy. *TP73* belongs to the family of p53-related proteins, which is involved in cell cycle arrest and apoptosis. Methylation of *TP73* has been reported in 94% of NKTCL and has been proposed as a biomarker to detect NKTCL involvement and metastasis [103]. *MYC* family genes encode multifunctional nuclear phosphoproteins that function as transcription factors to regulate expression of genes involved in cell cycle progression such as *CCNA2*, *CDKN1A*, and *CDKN2B*. Although frequent in hematopoietic and solid tumors, mutations, amplification, and translocation of this oncogene have not been found in NKTCL. However, *MYC* expression appears to be upregulated in the gene signature of NKTCL.

Adhesion and cell-to-cell interaction molecules may play an important role in tumor growth and homing in view of the particular tropism of NKTCL for extranodal sites. The molecular signatures reported for NKTCL in comparison with normal NK cells include overexpression of genes of the cadherin family (*CDH1*), of the integrin family (*VCAM1*, *ITGA7*, *ITGA9*, and *ITGB4*), and of the sialoadhesin family (*SIGLEC1*, *SIGLEC 9*, *SIGLEC11*, and *SIGLECP3*). Protocadherin 15 (*PCDH15*) was shown to be expressed ectopically by NKTCL cells and NKTCL-derived cell lines [104], and confirmed in gene expression profiling [24]. *PCDH15*, normally absent in the hematopoietic tissues, may be used by NK tumor cells to escape immunosurveillance, like *CDH1* recognized by the *KLRG1* inhibitory NK receptor [105].

Recently, AURKA, the Aurora kinase A or ST6, was reported as another potential target for NKTCL [25]. AURKA is a mitotic centrosomal protein kinase that controls chromosome segregation during mitosis [89, 106]. AURKA is activated by phosphorylation and could be detected in all human NK cell lines tested, validating its transcriptomic overexpression observed in NKTCL versus normal NK cells. In many other cancers, AURKA upregulation results in a phenotype characteristic of loss-of-function mutations of

TP53. Katayama et al. showed that *TP53* is phosphorylated by AURKA, inducing its ubiquitination by MDM2 and its proteasomal degradation [107]. Thus, AURKA is a key regulator of *TP53* pathway, and the AURKA inhibitor MK8751 induced cell cycle arrest and apoptosis in human cell lines, including NKTCL-derived cell lines [25]. AURKA represent, therefore, an interesting potential therapeutic target for NKTCL.

8. Conclusion

ANKL and NKTCL are EBV-associated malignancies of cytotoxic lymphocytes with poor prognosis and lack of efficient therapies. Their aggressive behavior and poor response to chemotherapy make of paramount importance the search for novel therapeutic targets in the treatment of these lymphomas. NKTCL is a rare disease although more frequent in Asia and South America, and the insufficient supply of tumor samples limits the development of an intense research in that field. In this context, malignant NK/T-cell lines represent valuable tools to study these pathologies [108]. Genome-wide studies have generated new data improving our understanding of the disease. Indeed, candidate tumor suppressor genes, such as *PRDMI*, *ATG5*, *AIM1*, or *HACE1*, which can be inactivated by deletion and by methylation, have been identified. The molecular signature of NKTCL is distinct from that of other T-cell lymphoma subtypes. Compared to normal NK cells, NKTCL is characterized by activation of several pathways—*PDGFRA*, *VEGFR*, *AKT*, *JAK-STAT*, and *NOTCH*—which might represent targets for novel therapeutic options. Before setting up clinical trials, extensive experimental validation of the potential target will have to be undertaken using the available models. In this respect, the study of tumor engrafting and development in immunocompromised mice injected with NKTCL cell lines or tumor fragments [82, 109] can be valuable models to test new potential drugs and their *in vivo* activity. One can hope that the efforts of the researchers working to understand this pathology will soon lead to progress in the treatment of these lymphomas.

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