Advances in multiple omics of natural-killer/T cell lymphoma

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Abstract

Natural-killer/T cell lymphoma (NKTCL) represents the most common subtype of extranodal lymphoma with aggressive clinical behavior. Prevalent in Asians and South Americans, the pathogenesis of NKTCL remains to be fully elucidated. Using system biology techniques including genomics, transcriptomics, epigenomics, and metabolomics, novel biomarkers and therapeutic targets have been revealed in NKTCL. Whole-exome sequencing studies identify recurrent somatic gene mutations, involving RNA helicases, tumor suppressors, JAK-STAT pathway molecules, and epigenetic modifiers. Another genome-wide association study reports that single nucleotide polymorphisms mapping to the class II MHC region on chromosome 6 contribute to lymphomagenesis. Alterations of oncogenic signaling pathways janus kinase-signal transducer and activator of transcription (JAK-STAT), nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), WNT, and NOTCH, as well as epigenetic dysregulation of microRNA and long non-coding RNAs, are also frequently observed in NKTCL. As for metabolomic profiling, abnormal amino acids metabolism plays an important role on disease progression of NKTCL. Of note, through targeting multiple omics aberrations, clinical outcome of NKTCL patients has been significantly improved by asparaginase-based regimens, immune checkpoints inhibitors, and histone deacetylation inhibitors. Future investigations will be emphasized on molecular classification of NKTCL using integrated analysis of system biology, so as to optimize targeted therapeutic strategies of NKTCL in the era of precision medicine.

Keywords: Natural-killer/T cell lymphomas, Genomics, Transcriptomics, Epigenomics, Metabolomics, Targeted therapy

Background

Natural-killer/T cell lymphoma (NKTCL) is a highly aggressive subtype of non-Hodgkin’s lymphoma with malignant proliferation of CD56+/cytoCD3+ lymphocytes [1, 2]. Epstein-Barr virus (EBV) is critically involved in NKTCL and evidenced by in situ hybridization for EBV-encoded small RNA [3]. As the most common extranodal lymphoma, NKTCL occurs predominantly in nasal/paranasal area (such as the nasal cavity, nasopharynx, paranasal sinuses, tonsil, Waldeyer ring, and oropharynx), with a geographic prevalence in Asian and South American populations [2]. NK and T cells share a common bi-potential T/NK progenitor [4]. Approximately 40% of NKTCL is identified as T cell-origin, characterized by rearrangements of T cell receptor (TCR) gene and expression of TCR protein [5]. As for other cytogenetic and genetic alterations, deletion of chromosome 6q21, as well as mutations of oncogenes (KRAS, NRAS, FAT4, and CTNNB) and tumor suppressor genes (TP53), are frequently observed in NKTCL [6–9]. However, the driven changes of NKTCL pathogenesis and their underlying mechanisms remain to be fully elucidated.

System biology, consisting of genomics, transcriptomics, epigenomics, and metabolomics, is a group of hallmark techniques in current cancer research and provides insights into the panorama view of biological processes under malignant progression [10, 11]. These omics methods have been successfully implicated not only to elucidate pathogenesis of human diseases, but also to identify prognostic and therapeutic biomarkers [12, 13]. Here, the application of system biology on identification of multiple omics aberrations and their potential clinical rationales are reviewed in NKTCL.
Genomic aberrations
The development of multiple omics studies on NKTCL are illustrated in Fig. 1. Using whole-exome sequencing and targeted sequencing, recurrent somatic gene mutations are identified in NKTCL, mainly as RNA helicase gene DDX3X, tumor suppressors (TP53, MGA, and BCOR), janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway molecules (JAK3, STAT3, and STAT5B), and epigenetic modifiers (MLL2, ARID1A, EP300, and ASXL3) [9, 14]. Of note, DDX3X mutants exhibit decreased RNA-unwinding activity, loss of suppressive effects on cell-cycle progression in NK cells, as well as transcriptional activation of nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways. Patients with mutations in DDX3X and TP53 have a poor response to anthracycline-based chemotherapy [14]. Functioned as a tumor suppressor, MGA gene inhibits MYC-dependent cell growth and malignant transformation through binding with MAX [15]. Somatic loss-of-function mutations of MGA have been observed in solid tumors and may lead to tumor development [16]. BCOR is also likely to play an important role as a tumor suppressor gene [17]. However, the pathogenic mechanism of MGA and BCOR has not yet been revealed in NKTCL. JAK3-activating mutations are involved in cytokine-independent JAK-STAT signaling pathway activation to enhance NKTCL cell proliferation [18, 19]. STAT3 mutations are associated with STAT signaling pathway activation, and confer high programmed death ligand 1 (PD-L1) expression, which may promote tumor immune evasion [20, 21]. Mutations in genes related to epigenetic modification of NKTCL include histone methylation (KMT2D), histone acetylation (EP300), histone deubiquitination (ASXL3), and chromatin remodeling (ARID1A) [22]. A case with extranodal EBV-negative NKTCL is reported to harbor KDM6A mutation, which is located on Xp11.2 and acts as an enzyme specifically demethylating H3K27 [23].

Through genome-wide association study, genetic variants affecting individual risk of NKTCL has been investigated, showing that single nucleotide polymorphisms mapping to the class II MHC region on chromosome 6, with rs9277378 located in HLA-DPB1 is the strongest contributor to lymphomagenesis (odds ratio 2.65) [24]. More recently, a hotspot mutation of ECSIT-V140A has also been identified in NKTCL patients with lymphoma-ekassociated hemophagocytic syndrome and poor prognosis [25].

Copy number variations (CNVs)
Accumulation of genomic imbalances is implicated in hematological malignancies inducing the activation of oncogenes or inactivation of tumor suppressor genes. As revealed by comparative genomic hybridization, 6q21 is frequently deleted in NKTCL, leading to the loss of tumor suppressor genes located in this region, including PRDM1, ATG5, AIM1, FOXO3, and HACE1 [26, 27]. PRDM1 is required for NK-cell maturation

Fig. 1 Milestones of multiple omics studies on NKTCL. This timeline describes key discoveries of genomic (whole-exome sequencing, genome-wide association study, and comparative genomic hybridization), transcriptomic (gene expression profile), epigenomic (mRNA expression profile and global promoter methylation analysis), and metabolomics (LC/MS-based metabolomics profile) studies in NKTCL.
and proliferation [28]. Mutation or methylation in PRDM1, ATG5, and AIM1 have been reported in NKTCL cell lines [29], while another study indicates that HACE1 is not directly related to NKTCL pathophysiology [30].

Besides, recurrent CNVs are observed in other regions of chromosomes, comprising of chromosomal losses (on 1p, 17p, and 12q) and gains (on 2q, 13q, and 10q) [31]. Involved chromosomal fragments may include candidate genes related to malignant transformation and invasion (SI00A16, LAMB1, LAMC1, COLIA2, and CTSB), cell-cycle progression (CCND2), JAK-STAT (AKT3, IL6R, and CCL2), and NF-κB (PRKCQ and TNFRSF21) signaling pathways [32]. More recently, other molecular clusters have been proposed, such as loss of 1q41.2 (TCRA loci), gain of 1q32.1-q32.3, and loss of Xp22.33 [33].

Transcriptional profiling
Based on gene expression profiling, integrations of JAK-STAT, NF-κB, and Akt signaling pathways contribute to genotoxic stress, angiogenesis, immunosuppression, and disease progression of NKTCL, as compared to normal NK cells [32, 34]. Activation of WNT and NOTCH signaling pathways are also enriched in NK-cell malignancies [35]. In accordance with CNV findings, downregulation of tumor suppressor genes in 6q21 (PRDM1, ATG5, AIM1) are confirmed by microarray analysis [27, 32]. As for individual genes, it is noteworthy that MYC induces upregulation of EZH2 and RUNX3, both of which exert cascade effect of transcriptional activation during lymphomagenesis [36, 37]. Using RNA sequencing technology, overexpression of KIR2DL4 is reported in malignant NK cells [38]. KIR2DL4 mediates NK-cell activation via inducing proliferation and survival pathways such as NF-κB and Akt, which may contribute to NKTCL pathogenesis [38].

Epigenetic signatures
In addition to mutations in epigenetic modifiers, differential expression of miRNAs plays a pathogenic role in NKTCL, through targeting cell-cycle-related genes, P53 and MAPK signaling pathways [39, 40]. Loss of miR-26 and miR-101 contribute to the overexpression of EZH2, while upregulation of miR-223 downregulates PRDM1 [36, 41]. EBV-encoded miRNAs have also been detected, including miRs-BART 1 to 22 of BamHI-A region rightward transcript (BART) family, as well as miRs-BHRF1-1, miRs-BHRF1-2, and miRs-BHRF1-3 of the BamHI fragment H rightward open reading frame 1 (BHRF1) family [42, 43]. Viral miRNAs are relatively less present in NKTCL than in nasopharyngeal carcinoma (2.3% of the total miRNA reads vs 5–19% in nasopharyngeal carcinoma) with unknown function [42, 44].

Meanwhile, NKTCL-associated dysregulated long non-coding RNAs have been identified, such as SNHG5, ZFAS1, and MIR155HG [45]. Among them, upregulation of ZFAS1 is implicated in stabilization of TP53, alterations of apoptosis and cell cycle, and activation of NF-κB signaling, while MIR155HG is downregulated by PRDM1 in NKTCL [45].

Promoter region hypermethylation has been investigated by global methylation assays, locus-specific validation of methylation, and methylation-specific polymerase chain reaction, demonstrating increased methylation and decreased gene expression with pathological and clinical significance, including PRDM1, ATG5, AIM1, BCL2L11, DAPK1, TET2, PTPN6, SOCS6, PTPRK, and ASNS [27, 46, 47]. Functionally, inactivation of TET2 may contribute to hypermethylation of global promoters in NKTCL [46]. PTPN6, SOCS6, and PTPRK negatively regulate JAK-STAT, suggestive an alternative mechanism responsible for activation of JAK-STAT signaling pathway [46–49].

Metabolomics profiling
Serum metabolic profile of NKTCL patients is distinct from that of healthy volunteers [50]. Briefly, 115 significantly altered serum metabolites are identified, predominately involving in pathways of amino acid metabolism [50]. As depicted by alanine, aspartate, and glutamate metabolism pathway in KEGG (Kyoto Encyclopedia of Genes and Genomes), nine of them are asparaginase-associated metabolites (alnine, aspartic acid, malic acid, ornithine, glutamate, glutamine, histidine, pantothentic acid, and succinic acid) and differently expressed in patients with good response to asparaginase, suggesting the reliance of malignant NK cells on extracellular amino acids. Based on serum metabolomics, our group has established a prognostic asparaginase-associated metabolic (AspM) score, including alanine, aspartate, glutamate, and succinic acid [50]. As a prognostic score independent of International prognostic index, as well as prognostic index of natural-killer lymphoma (PINK) or PINK in combination with peripheral blood EBV DNA, AspM score is easily attainable from peripheral blood and efficiently predicts response to asparaginase-based regimens [50].

Therapeutic strategies targeting multiple omics alterations
Schematic description of NKTCL pathogenesis and targeted therapeutic strategies are shown in Fig. 2. With the understanding of multiple omics alterations, clinical outcome of NKTCL has been significantly improved by new therapeutic strategies.

Different from metabolomic fingerprints of T and B cell lymphoma, NKTCL is characterized by dysregulated
amino acid metabolism, mainly as alanine, aspartate, and glutamate metabolism \cite{50}. Asparaginase and methotrexate are the most commonly used anti-metabolite agents, functioning through hydrolyzing extracellular asparagine or targeting folate, pyrimidine, and purine metabolism, respectively \cite{50,51}. For localized NKTCL, methotrexate, etoposide, dexamethasone, and peg-asparaginase (MESA) sandwiched with radiotherapy achieved complete remission (CR) rate of 89.5\% in 38 patients. The 2-year progression-free survival (PFS) and overall survival (OS) rate are 89.1\% and 92.0\% \cite{50}. These data highlight the role of targeting metabolic vulnerability in NKTCL.

Increased expression of cell cycle-related genes has been reported in NKTCL \cite{39}. Platinum, gemcitabine, and etoposide are cell cycle-specific DNA damaging agents \cite{52–54}, which are prevalently used in NKTCL chemotherapy. For advanced or relapsed/refractory NKTCL, CR rate of P-GEMOX (peg-asparaginase, gemcitabine, and oxaliplatin) is 51.4\% of 35 patients, with 2-year PFS and OS rate of 38.6\% and 64.7\% \cite{55}. In a randomized controlled, multicenter, and open-label clinical trial, DDGP (dexamethasone, cisplatin, gemcitabine, and peg-asparaginase) results in a CR rate of 71\%, as well as significant improvement in 2-year PFS and OS rate to 86\% and 74\% \cite{56}. Therefore, inhibition of cell-cycle progression is another key target in treating NKTCL \cite{57}.

Programmed death ligand 1 (PD-L1) is frequently up-regulated in NKTCL \cite{33}. Moreover, TP53 mutation, activation of STAT3 signaling pathway, and EBV-driven latent membrane protein-1 are all related to PD-L1 overexpression \cite{20,58,59}. Clinically, patients with NKTCL relapsed or refractory from 1-asparaginase-based regimens and allogeneic hematopoietic stem-cell transplantation respond well to the anti-programmed death-1 (PD-1) antibody pembrolizumab, with overall response rate (ORR) as 100\% \cite{60}. Favorable responses to pembrolizumab are also observed in another independent study with ORR as 57\% (4 out of 7 relapsed/refractory NKTCL) \cite{61}, indicating that PD-1 blockade is an important immunotherapy for NKTCL resistant to anti-metabolic and cytotoxic agents.

Histone deacetylase inhibitors serve as promising epigenetic agents, and phase II trials have been carried out in T cell lymphoma (including NKTCL), showing that 1 out of 2 enrolled NKTCL cases responds to Belinostat, while 3 out of 16 cases respond to Chidamide \cite{62,63}. 

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**Fig. 2** Schematic description of NKTCL pathogenesis and targeted therapeutic strategies. This illustration encompasses six hallmark mechanisms involved in NKTCL pathogenesis, which are closely related to targeted therapeutic strategies.
Since promoter region hypermethylation is present in NK/TCL, in vitro studies indicate that reversal of methylation by decitabine induces expression of key candidate genes involved in tumor suppressor (PRDM1), pro-apoptosis (BIM and SAPK), JAK-STAT pathway (SOCS6, ZFHX3, and PTPN6), and cell growth inhibition (CD300A) etc., leading to increased NK-cell death [27, 46].

ECSIT-V140A is associated with activation of NF-κB pathway, transcription, and secretion of pro-inflammatory cytokines. The immunomodulatory agent thalidomide prevents NF-κB from binding to the promoters of its target genes (including TNF and IFNG), and combined treatment of thalidomide and dexamethasone extends disease-free survival of two NK/TCL patients with hemophagocytic syndrome who express ECSIT-V140A for longer than 3 years [25]. Lenalidomide has also successfully been used in a patient with relapsed NK/TCL after autologous hematopoietic stem-cell transplantation [64].

Novel bio-agents are currently under pre-clinical studies. High-throughput drug sensitivity and resistance testing identify JAK inhibitor ruxolitinib to be highly effective across NK/TCL cell lines [65]. Therapeutic effect of a novel selective JAK3 inhibitor PRN371 has been recently confirmed in xenograft model harboring JAK3 activating mutation [66]. As mechanism of action, JAK3 inhibitors inhibit NK/TCL cell growth in an EZH2 phosphorylation-dependent manner, which functions as a transcriptional activator of NK/TCL. STAT3 inhibitor tofacitinib is active against STAT3-mutant NK/TCL cell lines [18], while JAK1/2 inhibitor partially against STAT3 and STAT5B mutations [21]. STAT3 activation confers PD-L1 overexpression, which can be downregulated by STAT3 inhibitors, alone or combined with PD-1/PD-L1 antibodies [20]. Combined treatment of LEE011 and ruxolitinib synergistically inhibit NK/TCL cell growth, suggesting that targeting of both CDK4/6 and JAK1/2 are promising treatment alternatives for NK/TCL [67].

**Perspectives**

Multiple omics analysis reveals genetic, epigenetic, transcriptomic and metabolic aberrations, which are not only associated with disease progression, but also response to clinical management. In the future, integration of system biology techniques should be further carried out to classify disease into subtypes of distinct molecular fingerprints, paving way for the implication of mechanism-based targeted therapy in NK/TCL.

**Abbreviations**

AspM: Asparaginase-associated metabolic score; BART: BamHI-A region rightward transcript; BHFR1: BamHI fragment H rightward open reading frame 1; CNV: Copy number variation; CR: Complete remission; EBV: Epstein-Barr virus; JAK-STAT: Janus kinase-signal transducer and activator of transcription; MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor-κB; NK/TCL: Natural-killer/T cell lymphoma; ORR: Overall response rate; OS: Overall survival; PD-1: Programmed death 1; PD-L1: Programmed death ligand 1; PFS: Progression-free survival; PINK: Prognostic index of natural-killer lymphoma; TCR: T cell receptor
Blucher AS, Choonoog K, Kulesz-Martín M, Wu G, McWeeny SK. Evidence-based precision oncology with the cancer targetome. Trends Pharmacol Sci. 2017;38(12):1085–99.

Jiang L, Gu ZH, Yan ZK, Zhao X, Xie YY, Zhang ZG, et al. Exome sequencing identifies somatic mutations of DDXXK in natural killer/T-cell lymphoma. Nat Genet. 2015;47(9):1061–6.

Ogawa H, Ishiguro K, Gaubatz S, Livingston DM, Nakatani Y. A complex with 6q21, is not involved in extranodal natural killer/T-cell lymphoma. Best Pract Res Clin Haematol. 2013;26(1):57–67.

Li Z, Xia Y, Feng LN, Chen JR, Li HM, Cui J, et al. Genetic risk of extranodal natural killer T-cell lymphoma. Tumour Biol. 2016;37(3):3589–99.

Kuo GC, Taw, Yee Kang T, Poon SL, Allen GE, Tan L, et al. Janus kinase 3-activating mutations identified in natural killer/T-cell lymphoma. Cancer Discov. 2012;2(7):591–7.

Song TL, Nairismagi ML, Laurinens Y, Lim XQ, Tan J, Li ZM, et al. Oncogenic activation of the STAT3 pathway drives PD-L1 expression in natural killer/T-cell lymphoma. Blood. 2018;132(11):1146–58.

Kucuk C, Jiang B, Hu X, Zhang W, Chan JK, Xiao W, et al. Activating mutations of STAT5B and STAT3 in lymphomas derived from gammadelta-T cells. Science. 2002;296(5570):1132–3.

Li Z, Xia Y, Feng LN, Chen JR, Li HM, Cui J, et al. Epstein-Barr virus-negative extranodal natural killer/T-cell lymphomas in nasal type. Am J Pathol. 2011;178(5):1869–81.

Ng SB, Yan J, Huang G, Selvarajan V, Tay YL, Lin B, et al. Disregulated microRNAs affect pathways and targets of biologic relevance in nasal-type natural killer/T-cell lymphoma. Blood. 2011;118(18):4919–29.

Zhang X, Ji W, Huang R, Li L, Wang X, Li L, et al. MicroRNA-155 is a potential molecular marker of natural killer/T-cell lymphoma. Tumour Biol. 2015;36(9):5601–12.

Li Z, Nong L, Zhang S, Zhao J, Ti H, Dong Y, et al. The downregulation of PRDM1/Blimp-1 is associated with aberrant expression of miR-223 in extranodal natural killer/T-cell lymphoma, nasal type. J Exp Clin Cancer Res. 2014;33(7).

Motsch N, Albes J, Irimi G, Zhu J, Barth S, Reineke T, et al. MicroRNA profiling of Epstein-Barr virus-associated NAT-cell lymphomas by deep sequencing. PLoS One. 2012;7(8):e42194.

Kawano Y, Iwata S, Kawada J, Gottoh K, Suzuki M, Tori Y, et al. Plasma viral microRNA profiles reveal potential biomarkers for chronic active Epstein-Barr virus infection. J Infect Dis. 2013;208(5):771–9.

Zhu YJ, Pflueh T, Motsch N, Barth S, Nicholls J, Grasser F, et al. Identification of novel Epstein-Barr virus microRNAs from nasopharyngeal carcinomas. J Virol. 2009;83(7):3333–41.

Baytak E, Gong Q, Akman B, Yuan H, Chan WC, Kucuk C. Whole transcriptome analysis reveals dysregulated oncogenic IncRNAs in natural killer/T-cell lymphoma and establishes MIR155HG as a target of PRDM1. Tumour Biol. 2017;39(5):1010428317701648.

Kucuk C, Hu X, Jiang B, Klinekabel D, Geng H, Gong Q, et al. Global promoter methylation analysis reveals novel candidate tumor suppressor genes in natural killer cell lymphoma. Clin Cancer Res. 2015;21(7):1699–711.

Chen YW, Guo T, Shen L, Wong KY, Tao Q, Choi WW, et al. Receptor-type tyrosine-protein phosphatase kappa directly targets STAT3 activation for tumor suppression in nasal NK/T-cell lymphoma. Blood. 2015;125(10):1589–600.

Hwang MN, Min CH, Kim HS, Lee H, Yoon KA, Park SY, et al. The nuclear localization of SOCS6 requires the N-terminal region and negatively regulates Stat3 signal transduction in nasal-type NK/T-cell lymphoma. J Immunol. 2009;182(7):3807–14.

Kawano Y, Iwata S, Kawada J, Gottoh K, Suzuki M, Tori Y, et al. Plasma viral microRNA profiles reveal potential biomarkers for chronic active Epstein-Barr virus infection. J Infect Dis. 2013;208(5):771–9.
55. Wang JH, Wang L, Liu CC, Xia ZJ, Huang HQ, Lin TY, et al. Efficacy of combined gemcitabine, oxaliplatin and pegaspargase (P-gemox regimen) in patients with newly diagnosed advanced-stage or relapsed/refractory extranodal NK/T-cell lymphoma. Oncotarget. 2016;7(20):29092–101.

56. Li X, Cui Y, Sun Z, Zhang L, Li L, Wang X, et al. DDGP versus SMILE in newly diagnosed advanced natural killer/T-cell lymphoma: a randomized controlled, multicenter, open-label study in China. Clin Cancer Res. 2016;22(21):5223–8.

57. Xiong J, Zhao WL. Targetable metabolic vulnerability in diffuse large B-cell lymphoma. EBioMedicine. 2018;28:5–6.

58. Biton J, Mansuet-Lupo A, Pecuchet N, Alifano M, Ouakrim H, Arrondeau J, et al. TP53, STK11, and EGFR mutations predict tumor immune profile and the response to anti-PD-1 in lung adenocarcinoma. Clin Cancer Res. 2018;24(22):5710–23.

59. Bi XW, Wang H, Zhang WW, Wang JH, Liu WJ, Xia ZJ, et al. PD-L1 is upregulated by EBI-driven LMP1 through NF-kappaB pathway and correlates with poor prognosis in natural killer/T-cell lymphoma. J Hematol Oncol. 2016;9(1):109.

60. Kwong YL, Chan TSY, Tan D, Kim SJ, Poon LM, Mow B, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood. 2017;129(7):2437–42.

61. Li X, Cheng Y, Zhang M, Yan J, Li L, Fu X, et al. Activity of pembrolizumab in relapsed/refractory NK/T-cell lymphoma. J Hematol Oncol. 2018;11(1):15.

62. O’Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduin J, et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. J Clin Oncol. 2015;33(23):2492–9.

63. Shi Y, Dong M, Hong X, Zhang W, Feng J, Zhu J, et al. Results from a multicenter, open-label, pivotal phase II study of chidamide in relapsed or refractory peripheral T-cell lymphoma. Ann Oncol. 2015;26(8):1766–71.

64. Wang L, Wang ZH, Chen XO, Wang KF, Huang HQ, Xia ZJ. First-line combination of GELOX followed by radiation therapy for patients with stage I/II ENKTL: an updated analysis with long-term follow-up. Oncol Lett. 2015;10(2):1036–40.

65. Dufva O, Kankainen M, Kekka T, Sekiguchi N, Awad SA, Eldfors S, et al. Aggressive natural killer-cell leukemia mutational landscape and drug profiling highlight JAK-STAT signaling as therapeutic target. Nat Commun. 2018;9(1):1567.

66. Nairismagi M, Gerritsen ME, Li ZM, Wijaya GC, Chia BKH, Laurensia Y, et al. Oncogenic activation of JAK3-STAT signaling confers clinical sensitivity to PRN371, a novel selective and potent JAK3 inhibitor, in natural killer/T-cell lymphoma. Leukemia. 2018;32(5):1147–56.

67. Hee YT, Yan J, Nizetic D, Chng WJ. LEE011 and ruxolitinib: a synergistic drug combination for natural killer/T-cell lymphoma (NKTL). Oncotarget. 2018;9(61):31832–41.