00410 Oncogenic Activation of STAT3 Pathway Drives PD-L1 Expression in Natural Killer/T Cell Lymphoma

Yurike Laurensia[1], Song LinLin Tammy[1], Maarja-Liisa Nairismägi[1], Lim Jing-Quan[1], Tan Jing[1], Li Zhi-Mei[1], Pang Wan Lu[1], Atish Kizhakeyil[2], Giovani Claresta Wijaya[1], Huang Da-Chuan[1], Sanjanaa Nagarajan[1], Chia Kuan Hui Burton[1], Cheah Ming Zhe Daryl[1], Liu Yan-Hui[3], Zhang Fen[3], Rao Hui-Lan[4], Tiffany Tang[1], Nicholas-Francis Grigoropoulos[5], Ng Siok-Bian[6],Chng Wee-Joo[6], Teh Bin Tean[1], Tan Soo-Yong[6], Navin-Kumar Verma[2], Fan Hao[7], Lim Soon Thye[1], Ong Choon Kiat[1]

[1]National Cancer Centre Singapore, [2]Nanyang Technological University, [3]Guangdong General Hospital, [4]Sun Yat-Sen University Cancer Center, [5]Singapore General Hospital, [6]National University of Singapore, [7]A*STAR

Aims: The aim of the study is to determine the prevalence and therapeutic relevance of JAK/STAT pathway alterations in peripheral T cell lymphoma (PTCL) and NK/T cell lymphoma (NKTL).

Methodology: To determine the involvement of JAK/STAT pathway, targeted capture sequencing was performed with a customized probe set of 188 genes in 171 PTCL and NKTL cases from Singapore and China. The functional and structural characterization of STAT3 was explored by immunohistochemistry profiling in NKTL patients tumor tissues and in vitro experiments with BA/F3 and NK-S1 cell line that stably express wild-type STAT3 and novel STAT3 mutations.

Result: A total of 272 somatic mutations in 101 genes were identified and recurrent mutations were most frequently located in STAT3 and TP53 (15%) followed by JAK3 and JAK1 (6%) and SOCS1 (4%). A high prevalence of STAT3 mutation (21%) was observed specifically in NKTL. Novel STAT3 mutations (p.D427H, p.E616G, p.E616K and p.E696K) were shown to increase STAT3 phosphorylation and transcriptional activity of STAT3 in the absence of cytokine, in which p.E616K induced PD-L1 expression. Consistent with these findings, PD-L1 was overexpressed in NKTL cell lines harboring hotspot STAT3 mutations and NK-S1 cell lines with overexpression of p.E616K and p.E616G. A positive correlation between PD-L1 and p-STAT3 expression was observed in NKTL tumor tissues. Conversely, STAT3 silencing and inhibition decreased PD-L1 expression in STAT3 mutant NKTL cell lines.

Conclusion: In summary, alterations in JAK/STAT signaling pathway are highly prevalent in PTCL and NKTL where STAT3 and TP53 are the most frequently mutated genes. We identified novel activating STAT3 mutations (p.D427H, p.E616G, p.E616K and p.E696K) that might be promising targets for inhibition in the treatment of NKTL. We demonstrated for the first time that STAT3 regulates PD-L1 expression in NKTL, thus providing rationale for combinations of targeted therapies and immune checkpoint blockade inhibitors in NKTL and possibly PTCL.