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Selective expression of KIR2DL4 for improved diagnosis and as a potential therapeutic target in natural killer/T cell lymphoma

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Extra-nodal natural killer/T-cell lymphoma, nasal type (NKTCL) is an uncommon but aggressive malignancy associated with significant diagnostic challenges. NKTCLs may occasionally be misdiagnosed as inflammatory diseases that require different disease management and therapeutic strategies. Previous reports indicated NKTCLs can be misdiagnosed as tuberculous meningitis [1], fungal infections [2], or polymyositis [3]. This may result from the frequent small biopsies, massive necrosis, angiocentric tumor infiltrates and unfamiliarity with the condition. Another challenge is related to lack of clonal diagnostic biomarkers for NKCLs, in contrast to B or T-cell malignancies that have uniquely rearranged antigen receptor genes. Therefore, Küçük, *et al.* recent report [4] that has shown selective expression of KIR2DL4 in more than half of the NKTCL cases often with lack of expression of other KIRs may provide opportunity for more accurate diagnosis.

Killer-cell immunoglobulin like receptors (KIR) belong to a family of polymorphic but homologous genes [5] such that specific measurements of KIR genes, including KIR2DL4 expression are often unreliable using DNA microarray due to non-specific hybridization. Evaluation by antibodies may similarly be compromised due to cross-reactivity. Consequently, RNA-Seq applied by Küçük, *et al.* on NKTCL tumors showed the advantage of this NGS-based method in terms of specificity of measurement of highly homologous gene families such as KIR family genes when coupled with careful analytical approaches. Given the continuously decreasing prices of RNA-Seq in the market, it may be possible in the near future to observe the integration of this NGS-based methodology in routine clinical practice to facilitate NKTCL diagnosis.

Future studies with larger series will need to be evaluated to address whether there is prognostic value of KIR2DL4 expression in addition to its diagnostic utility. Also, it will be interesting to determine the frequency and expression level of KIR2DL4 and other KIRs in extra-nasal NKTCLs that shows markedly worse prognosis compared to nasal NKTCLs [6].

Another interesting finding presented by Küçük, *et al.* is the growth inhibition observed after shRNA-mediated knock-down of KIR2DL4 in two malignant NK-cell lines. This observation suggests that KIR2DL4 may transmit activating/survival signals to the neoplastic cells. This KIR is a cell surface receptor normally regulated through engagement with their cognate ligands (e.g. HLA-G) available in the extra-cellular environment. It is not clear whether the regulation of KIR2DL4 only depends on extra-cellular factors or cell-intrinsic mechanisms are present in neoplastic cells. In support of the latter possibility, KIR2DL4 was reported to be present also in endosomes where it can generate signals that can contribute NK-cell activation [7]. More importantly, KIR2DL4 was recently shown to self-associate based on comprehensive characterization of its molecular structure raising the possibility of induction of signal transduction after oligomerization [8]. Altogether these results suggest that KIR2DL4 expression may have biological implications in addition to its potential as a molecular diagnostic marker, and future investigations with higher number of NKTCL patient samples and in-depth functional analysis will be critical to address these possibilities.

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