

# Impact of multiplicity of functional KIR-HLA compound genotypes on hepatocellular carcinoma

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**Abbreviations:** ADCC, antibody-dependent cell-mediated cytotoxicity; HCC, hepatocellular carcinoma; HLA, human leukocyte antigen; KIR, killer immunoglobulin-like receptors.

Natural killer (NK) cells are potential immune components against hepatocellular carcinoma (HCC) after curative hepatectomy. Patients at high risk of HCC recurrence can be identified by quantifying NK cell licensing. Therefore, therapeutic strategies that manipulate NK cell activity may possibly improve the prognosis of HCC patients.

NK cells are key components of the innate immune system that act against infectious and neoplastic cells. NK cell activation is dependent upon the inhibitory-activating receptor equilibrium. Killer cell immunoglobulin-like receptors (KIRs) are the most polymorphic among these receptors. They contribute to receptor–ligand interactions that determine NK cell responses by recognizing specific human leukocyte antigen (HLA) class I allotype ligands.

In 2006, Anfossi et al. reported an educational mechanism for human NK cells that involves self-specific inhibitory KIR and cognate HLA ligand interactions. This mechanism leads NK cells to acquire a higher resting response capacity,<sup>1</sup> consistent with the NK cell “licensing” mechanism in mice.<sup>2</sup> The polymorphic genes for KIRs and their cognate HLA ligands generate diverse immune responses. Ligand specificities for five inhibitory KIRs and the different strengths of licensing effects through different KIR–HLA ligand interactions have been defined. Thereafter, Yu et al. demonstrated that NK cells, which express multiple inhibitory KIRs for self-HLA ligands within variegated NK cell

repertoires, show a synergistic effect of licensing, i.e., the expression of progressively higher numbers of self-reactive inhibitory KIRs is correlated with increased effector capacity.<sup>3</sup> This quantitative effect of NK cell licensing has been verified consistently in mice by analyzing the functional influence of the multiple interactions of self-major histocompatibility complex (MHC)-specific inhibitory receptors.<sup>4</sup> Recently, Beziat et al. also showed a linear effect of KIR gene copy number variation and HLA ligands on the overall functional responsiveness of the NK cell repertoire by analyzing KIR–HLA genotypes of healthy human volunteers.<sup>5</sup> Despite the accumulating evidence suggesting a quantitative effect of NK cell licensing in basic studies, its clinical impact on neoplastic diseases has never been demonstrated. This year, we were the first to report the impact of multiplicity of functional KIR–HLA compound genotypes on HCC recurrence after curative hepatectomy.<sup>6</sup> The presence of *KIR2DL1-C2*, *KIR2DL2-C1*, *KIR3DL1-BW4*, or *KIR3DL2-A3/11*, functional compound genotypes that intrinsically license NK cells, did not markedly affect

HCC recurrence. However, the cumulative risk of recurrence in patients with at least three compound genotypes (highly licensed patients) was significantly lower than that in patients with one or two compound genotypes (poorly licensed patients), suggesting that the effect of NK cell licensing on HCC recurrence is quantitative. This result matches the previously postulated theory that the number and type of host MHC class I alleles quantitatively tune the responsiveness of individual NK cell subsets expressing the corresponding KIR.<sup>5</sup> Highly licensed patients may equip NK cells with more vigorous immune-surveillance activity to act as potent constitutive immune effectors against both intrahepatic metastasis and *de novo* carcinogenesis, as compared to poorly licensed patients (Fig. 1).

We have previously shown that the distribution of NK cells is anatomically biased, e.g., NK cells are quite abundant in human livers.<sup>7</sup> Functionally, liver NK cells display a significantly higher cytotoxic activity against neoplastic cells, including against HCC, through a tumor necrosis factor-related apoptosis-inducing ligand-mediated mechanism,

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cytotoxicity and antibody-dependent cell-mediated cytotoxicity (ADCC) to lyse antibody-coated cells. Since NK cells contribute to ADCC, therapies combining NK cells and antibody targeting have the added advantage of local activation of NK cells at the tumor site via CD16

activation. A previous report demonstrated that unlicensed NK cells formed the predominant subset of NK cells, which have potent ADCC due to their lack of inhibitory receptors for self.<sup>10</sup> Hence, the impact of NK cell licensing on the therapeutic outcome of antibody

targeting agents may need to be elucidated through further studies.

#### Disclosure of Potential Conflicts of Interest

The authors have declared no conflicts of interest.

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