# Transcriptomic Profiles of NK Cells in Patients With Hepatocellular Carcinoma: An Exploratory Framework to Unlock Their Therapeutic Potential

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Natural Killer (NK) cells -both circulating (cNK) and liver resident (lr-NK) - are a major component of innate host defense against Hepatocellular carcinoma (HCC). NK cell dysfunction is associated with the development and progression of HCC. Using single cell RNA sequencing data, we analyzed the gene expression profiles (GEP) of NK cell populations in four patients with HCC based on their location in the liver. We isolated and compared NK cell transcriptomes among samples from specific sites in the liver: tumor core, tumor periphery, and adjacent normal liver. Seven NK cell clusters were identified, reflecting differences in phenotype and maturity. The GEP of NK cells in tumor core and periphery were similar, but distinct compared to those from adjacent normal liver. NK cells in tumor core and periphery were predominantly lr-NK cells and mature cNK cells while the principal constituent in adjacent normal liver was a unique cluster of NK cells that harbored markers of cytotoxicity and immune exhaustion. Differential expression of genes regulating key immunomodulatory pathways were noted between lr-NK cells in tumor core vs. normal liver and tumor periphery vs. normal liver. The functional significance of differences in GEP noted between NK cells in tumor core and tumor periphery compared to adjacent normal liver needs further exploration to elucidate the complex immune milieu of HCC. More importantly, the markers of cytotoxicity and immune exhaustion noted in a subset of NK cells excluded from the tumor core highlights the therapeutic potential of NK cell immune modulation in HCC.

**Awards Won:**