Mechanisms underlying human placental CD34+ cell-derived natural killer cell cytotoxicity against glioblastoma

Tanel Mahlakõiv, Bhavani Stout, Valentina Ruseva, Irene Raltman, Lin Kang, Robert Harii, Xiaokui Zhang and William van der Touw

Celularity, Inc. Warren, New Jersey, United States

INTRODUCTION

Background

Natural killer (NK) cells are innate immune cells with a critical role in immune surveillance against cell transformation and tumor development. NK cells express an array of unique activating and inhibitory receptors whose aggregate signaling determine the activation of NK cell effector function. Adoptive transfer of NK cells has demonstrated the potential to induce antitumor responses in the clinic. Celularity has developed a platform for generating cytotoxic NK cells from placental CD34+ cells (PNK cells) for adoptive cancer immunotherapy. Although PNK cells demonstrate cytotoxicity against diverse cancer cell types, their activating mechanisms are little characterized. In this study, we explore the contribution of specific signaling pathways and upstream NK cell receptors involved in PNK cell cytotoxicity against glioblastoma multiforme (GBM) cell targets.

RESULTS

Figure 3. PNK cells highly express genes encoding the cytotoxic machinery

Figure 4. PNK cells express a range of natural killer cell receptors

Figure 5. JNK and PI3K signaling regulate PNK cytotoxicity against GBM

CONCLUSIONS

• PNK cells efficiently kill GBM cell lines in vitro.
• Transcriptional and phenotypic characterization demonstrated that PNK cells express the cytotoxic machinery at a high level.
• Contact with GBM cells activates ERK and PI3K signaling pathways in PNK cells.
• PI3K and JNK pathways in PNK cells mediate cytotoxicity against GBM cell line targets.
• PI3K pathway is activated downstream of NKG2D receptor in PNK cells.
• NKG2D plays an important role in triggering cytotoxicity against GBM cells.
• These data establish the rationale for further investigating receptor-ligand interactions that directly modulate PI3K and JNK activity in PNK cells and support PNK cell development for clinical studies in GBM patients.