ABSTRACT

Natural killer (NK) cells are an essential part of immune system, providing self-surveillance of virally infected, stress transformed or cancerous cells. NKR-P1 receptors and their ligands from *clec2* gene family represent an alternate missing-self recognition system of NK cells based on interaction of highly related C-type lectin-like receptors. Human NKR-P1 has been described more than twenty years ago but still remains the sole human orthologue of this receptor family, particularly numerous in rodents. On binding to its cognate ligand LLT1, NKR-P1 can relay inhibitory or co-stimulatory signals. Although being interesting targets for their potential role in tumor immune evasion and autoimmunity, nature of their interaction is still unclear.

To elucidate the architecture of their interaction, we developed a generally applicable method for recombinant expression of human NKR-P1 and LLT1 and their homologues based on transfection of HEK293S GnTI$^-$ cells. Further, we described a stabilizing mutation His176Cys, that enables for expression of highly stable and soluble LLT1. Finally, we have crystallized LLT1 and human NKR-P1 in different glycosylation states both as individuals and in complex. While both structures of LLT1 and NKR-P1 follow the classical C-type lectin-like superfamily fold, contrary to LLT1, NKR-P1 forms a unique homodimer centered by its helix α1 that is similar to Dectin-1. Moreover, in the structure of their complex the α1/α2-centered dimers alternate in bivalent interaction of two distinct types. While the first is similar to manner of interaction of related complexes of human NKp65:KACL and mouse NKR-P1B:m12, the second one is unique.