学 位 論 文 の 要 約

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学 位 論 文 題 名

Molecular mechanism of ligand recognition by the immune activation receptor LILRA2
（免疫活性化受容体 LILRA2 によるリガンド認識の分子機構）

Human leukocyte immunoglobulin-like receptors (LILRs) have functions in infections, autoimmune diseases, and cancer. LILRs typically regulate immune activation by binding to the human leukocyte antigen class I molecules (HLA-I). As a member of the LILR family, LILRA2 was reported to recognize the bacterially N-terminus truncated Ig (N-truncated) for the induction of innate immune response. Ligand A2L, which was referred as one vital factor in human blood, was recently reported to bind to LILRA2 for the activation of immune cells. However, the detailed molecular mechanisms of this interaction remain unclear. In this study, we revealed the molecular mechanisms of A2L recognition by LILRA2 utilizing several biophysical techniques.

Surface plasmon resonance analysis elucidated the specifically of LILRA2 binds to A2L with weak affinity (K_D = 9.9 μM) and fast kinetics. However, oligomeric A2L exhibited a significantly enhanced interaction to immobilized LILRA2 due to avidity effects. This result suggests that cell-surface expressed LILRA2 rapidly recognizes A2L through specific cross-linking that triggers immune activation. Mutagenesis analysis further identified the crucial sites of both LILRA2 and A2L that involved in the interaction. A new binding mode that distinct from previously reported ones in LILR family was demonstrated.

In structural analysis, a low-resolution cryo-EM map was reconstructed for LILRA2-Fab complex to obtain structural information regarding the ligand binding modes of LILRA2. The outlines of each domain could be roughly identified while the details were not clear.

With AlphaFold 3 server, predicted models were displayed for both LILRA2-A2L complex and LILRA2-Fab complex, providing support information for structural analysis of LILRA2 ligand recognition mechanisms.

These results provide detailed insights into the molecular regulation of LILR-mediated immune responses targeting its ligands, which demonstrates potential contributions to novel therapeutics development and innovative drug discovery.