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Structural studies of human RIG-I, a cytosolic dsRNA recognition protein

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The structure of the human TLR3 ectodomain (ECD) was determined to 2.1 Å resolution and revealed a large horseshoe-shaped, right-handed solenoid structure comprised of 23 leucine-rich repeats (LRRs). The inner concave surface is formed from 25 parallel b-strands that makes a highly curved, continuous b-sheet that spans 270 ^{o} of arc. Seven conserved hydrophobic residues in this motif form a tight hydrophobic core of the solenoid structure and conserved asparagine at position 10 makes extensive hydrogen-bonding networks. TLR3 ECD has 15 potential glycosylation sites and electron density for carbohydrate is observed for 8 of these sites. When oligomannans are modeled into all 15 predicted sites, most of the protein surface, with the exception of one side face, is covered with carbohydrates. The inner concave surface of TLR3 has two glycosylation sites and revealed predominantly negative charges when calculated by the program GRASP, that makes it an unlikely binding site for dsRNA. The glycosylation-free face contains two surface patches with a dense cluster of positively charged residues and a TLR3-specific insertion in LRR12 that could play a role in dsRNA binding. This face also contains a highly-conserved surface patch that coincides with a putative homodimer interface observed in the crystal. Based on the location of glycosylation sites, the electrostatic surface potential, the TLR3-specific insertion and the dimer formation, a model for the dsRNA binding site and mode of signal transduction was proposed. Comparison with recently determined TLR4 and TLR1/2 structures will be discussed.