Dll1 and Dll4 differently require their extracellular domains for triggering Notch signaling

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Delta-like (Dll) 1 and Dll4 differently function as Notch ligands in a context-dependent manner. As these ligands share structural properties, the molecular basis for their functional difference is poorly understood. Here, we investigated the superiority of Dll4 over Dll1 with respect to induction of T cell development using a domain-swapping approach in mice. The DOS motif, shared by Notch ligands—except Dll4—contributes to enhancing the activity of Dll for signal transduction. The module at the N-terminus of Notch ligand (MNNL) of Dll4 is inherently advantageous over Dll1. Molecular dynamic simulation revealed that the loop structure in MNNL domain of Dll1 contains unique proline residues with limited range of motion. The Dll4 mutant with Dll1-derived proline residues showed reduced activity. These results suggest that the loop structure—present within the MNNL domain—with a wide range of motion ensures the superiority of Dll4 and uniquely contributes to the triggering of Notch signaling.