A220 · Structural Modeling Identifies a Putative, MIF-Independent CD74–IFNGR1 Interface in IFN-γ Signaling

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CD74 deletion abolishes IFN-γ–driven allograft rejection (median survival >100 days vs. 7 days) and reduces T-cell pSTAT1 signaling by ~50% despite unchanged surface IFNGR1, indicating a receptor-proximal defect that persists in MIF-deficient mice, demonstrating that the canonical CD74 ligand is dispensable. To identify a structural mechanism, we integrated sequence analysis, experimentally resolved receptor structures, multimeric modeling, multi-platform protein–protein docking, interface energetics, and molecular dynamics. IFNGR1–CD74 sequence comparison revealed 24.0% global and 29.5% local identity over a 78-residue window. Mapping this region onto IFN-γ receptor complexes 6E3K and 6E3L identified an extracellular IFNGR1 segment (~129–221; predominantly 162–221) overlapping the experimentally defined IFN-γ/IFNGR1 interface at 25/75 and 24/72 resolved residues, respectively, with approximately half of these residues solvent-exposed. Independent HDOCK, ClusPro, and HADDOCK docking converged on this region, supporting a reproducible topology involving multiple CD74 protomers. HDOCK favored CD74 alone over CD74–MIF (−348.32 vs. −275.48), arguing against an MIF requirement for the predicted association. Interface energetics identified 16 dominant CD74–MIF hotspots ($\Delta G \leq -10$ kcal/mol), with stabilization correlated with solvent burial ($R^2=0.79$, $p<0.01$). Complementary 200-ns MD supported interface persistence: backbone RMSD remained below 3 Å, while 68% of candidate interface residues maintained contacts for >50% of the trajectory. Together, these orthogonal analyses identify a structurally plausible, multivalent CD74–IFNGR1 association overlapping the physiological IFN-γ-binding interface, providing a structural correlate for the MIF-independent receptor-proximal defect and nominating residues for experimental validation.