Degree in Medicine and Surgery

BSc in Biomedical Engineering

Decoding the CHI3L1-RAGE Immunosuppressive Complex: Integrative Structural and Coevolutionary Insights into HER2+ Breast Cancer Resistance

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Abstract

Introduction: In HER2$^+$ breast cancer, resistance often evolves faster than intervention. Amid this complexity, we identified a structurally defined immune checkpoint: the interaction between chitinase-3-like protein 1 (CHI3L1) and the receptor for advanced glycation end-products (RAGE). This thesis rests on a central proposition: that structure *is* function, and both are outcomes of molecular co-evolution. Our aim was not only to characterize this interaction, but to resolve its architecture and logic as a basis for therapeutic intervention.

Methods: To that end, we designed an integrative strategy that reflects the multidimensional nature of such a system. Biophysical measurements quantified affinity and explored stoichiometry and glycosylations; crystallographic experiments, though failing to capture the complex, successfully resolved CHI3L1's apo structure. To close the gap, we implemented a deep exploration of AlphaFold-Multimer predictions, systematically optimized across seeds and alignments.

Results: The result was a high-confidence atomic model of the CHI3L1-RAGE complex (multi = 0.880; actifpTM = 0.920), revealing a chemically precise interface: the positively charged FG-loop of RAGE inserts into CHI3L1's conserved glycan-binding groove, stabilized by specific cation-π contacts. This interaction induces a conformational shift in Trp99, a gatekeeper residue already known to reorient upon glycan binding.

Interpretation: The model suggests a mechanistically elegant form of antagonism: CHI3L1 acts as a structural blocker of the oligomerization of RAGE required for downstream cytotoxic signaling. Rather than competing for a site, it locks the receptor in a non-signaling conformation. This architecture also exposes a deeper evolutionary pattern: RAGE, a modern innate immune sensor, appears to have co-opted an ancient microbial-recognition module for internal regulation. The dual selective pressure on CHI3L1's groove, binding both non-self glycans and self immune partners, explains its conservation across deep evolutionary time.

Conclusion: This work transforms a diffuse resistance mechanism into a structurally tractable target. It provides a template for rational inhibitor design, and a conceptual framework for decoding immune regulation through structure. Within complex biological systems, architecture can be the clearest language. Evolution has already written the code. Our task is to read it.