Conservation of Allosteric Secondary Binding Sites Across Human C-type Lectins

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Due to their integral role in a wide range of physiological processes, C-type lectins (CTLs) represent attractive targets for diverse therapeutic interventions [1]. Yet, owing to their often shallow and polar carbohydrate binding site, the number of selective chemical probes remains limited [2]. In this context, previous studies indicated the presence of distal allosteric secondary sites in several CTLs with the potential of increased druggability and selectivity while simultaneously modulating the receptors activity [3–5].

Here, we computationally predict and characterize allosteric secondary sites across human CTLs. For this, we integrated established tools into a Python-based workflow that features (i) structural alignment of available CTL structures, (ii) pocket prediction, (iii) evaluation of allosteric potential of each pocket using an elastic network model (ENM)-based method and (iv) a sequence-based co-evolutionary approach. Density-based clustering of the resulting pocket ensemble enabled identification of 20 small, but structurally conserved pocket locations, of which at least four were predicted to possess allosteric potential. Additionally, comparison with experimental data showed overlap of several clusters with binding sites for endogenous and synthetic ligands as well as protein-protein interaction interfaces. While experimental validation will be necessary, these observations point towards an evolutionary conserved function of allosteric pockets across CTLs that could be leveraged as a new modality for targeting this protein family.

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