Physicochemical and Structural Characterisation of Cation-Mediated Polysaccharide Aggregation in Microbial Capsules and Its Implications for Therapeutic Targeting

Raja, Sindhoora (School: National Public School, Indiranagar)

Cryptococcus neoformans—a pathogenic yeast—poses a severe risk to immunocompromised individuals. Its polysaccharide capsule, primarily glucuronoxylomannan, is its chief virulence factor. Calcium-mediated interactions influence capsule assembly and immune evasion, yet molecular mechanisms remain unclear. Understanding them could provide novel therapeutic targets. This study examines how calcium selectively interacts with glucuronic acid in the capsular polysaccharide, driving aggregation and immune evasion. Given calcium-dependent biofilm formation and capsule assembly in other pathogens, these findings have broad implications. DOSY NMR measured calcium-induced changes in glucuronic acid diffusion, estimating molecular weight shifts via the Stokes-Einstein equation. DLS assessed particle aggregation. ATR-FTIR spectroscopy identified stable calcium-glucuronic acid interactions through spectral shifts in the carbonyl region. DFT predicted calcium coordination preferences and structural effects. Enthalpy changes were also calculated when divalent cations reacted with D-GlcA, D-GlcA(-) and solvated D-GlcA. Merck force fields mapped energy surfaces of monosaccharides and examined water-mediated stability. This research shows that Ca ions uniquely induce glucuronic acid aggregation, strengthening capsule stability—unlike Mg, Sr, and Cd ions. Divalent cation bridging occurs within and between capsules. DFT structures of aqueous Ca, Mg, Sr, and Cd complexes with deprotonated glucuronic acid, reported here for the first time, indicate bidentate bonding is preferred for one to three ligands. Targeting calcium-mediated aggregation could disrupt capsule integrity in C. neoformans and similar pathogens. Future work will explore antimicrobial strategies exploiting this mechanism.

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