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Human Protein Galectin-3 Blocks Dengue Virus Entry and Boosts Innate Immune Signaling

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A new study published in Virology Journal shows that galectin-3 -- a naturally occurring human sugar-binding protein -- acts as a built-in defense factor against dengue virus by latching onto sugar chains on the virus's outer shell and amplifying early immune warning signals. Led by researchers Zhi-Sheng Yang, Sheng-Fan Wang, and colleagues, the work demonstrates that extracellular galectin-3 dose-dependently reduces Dengue virus serotype 2 (DENV-2) infectivity while boosting pro-inflammatory NF- B signaling inside host cells.

Dengue virus infects tens of millions of people each year across tropical and subtropical regions, yet no widely effective direct-acting antiviral drug is currently approved for clinical treatment. Understanding how human host proteins naturally slow the virus down offers a promising blueprint for host-directed therapies that strengthen the body's own defenses.

How Galectin-3 Blocks Viral Entry

To infect a human cell, dengue virus relies on its outer envelope (E) glycoprotein -- a surface protein studded with branching sugar molecules called glycans -- to attach to receptors on the cell membrane . Galectin-3 belongs to a family of immune proteins known as lectins, which specialize in recognizing and binding specific carbohydrate structures.

Using cell-culture assays and biochemical binding experiments, the researchers found that galectin-3 binds directly to glycan structures on the DENV-2 envelope glycoprotein, including interactions involving the Asn67 glycosylation site. Once galectin-3 coats those viral surface sugars, the virus can no longer attach efficiently to host cells or complete entry, sharply lowering the number of new infectious viral particles produced.

| Host-Pathogen Mechanism | | Observed Experimental Effect | | Biological Outcome |

| Extracellular Galectin-3 | | Dose-dependent drop in DENV-2 infectivity | | Fewer infectious viral progeny released |

| Envelope Glycan Binding | | Targets E-protein sugar chains (including Asn67) | | Physically blocks viral attachment and cell entry |

| NF- B Immune Signaling | | Upregulates IL-6, IL-8, and TNF cytokines | | Accelerates early innate antiviral immune alert |

| Galectin-3 Deficiency / Suppression | | DENV-2 lowers endogenous galectin-3; loss worsens disease | | Highlights role as a natural host restriction factor |

Dual Action: Physical Shielding and Immune Alarm

Galectin-3 does more than act as a molecular shield outside the cell. The study shows that galectin-3 also enhances NF- B signaling -- a central cellular switch that turns on genes involved in inflammation and antiviral defense. When galectin-3 is present during DENV-2 exposure, cells upregulate key immune signaling molecules, including interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor (TNF), helping recruit and activate immune responses against the invading virus.

Interestingly, the researchers also observed a biological tug-of-war between the virus and the host. Active DENV-2 infection tends to drive down the host's own endogenous galectin-3 levels, whereas animal and cell-culture models lacking galectin-3 experience more severe viral infection. Together, those findings indicate that suppressing galectin-3 helps the virus gain a foothold, while restoring or supplementing it tilts the balance back toward host protection.

Implications for Host-Directed Dengue Therapies

Because dengue virus exists as four distinct serotypes and evolves rapidly under immune pressure, drugs that target viral enzymes directly can face resistance hurdles. By contrast, targeting conserved structural features such as envelope glycans -- or boosting natural host restriction factors like galectin-3 -- could offer broader protection across viral variants.

The authors note that careful preclinical work will be needed before translating galectin-3 biology into treatments, particularly because excessive pro-inflammatory cytokine signaling can contribute to severe dengue symptoms if not tightly controlled. Even so, identifying galectin-3 as a dual-acting restriction factor that both blocks viral entry and primes innate immunity adds an important piece to the puzzle of human defense against mosquito-borne flaviviruses.

References & Primary Sources

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