SELECTIVE BINDING OF IL-1α TO ISLET HEPARAN SULFATE ENHANCES IL-1 RECEPTOR ACTIVATION

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Interleukin-1α (IL-1α) and interleukin-1β (IL-1β) are key mediators of islet inflammation and β-cell dysfunction. While both cytokines signal through the IL-1 receptor type I (IL-1RI), IL-1α functions as an alarmin and is actively involved in early inflammatory responses [1]. Heparan sulfate, a sulfated glycosaminoglycan (GAG) present on the cell surface and in the extracellular matrix, is known to regulate protein activity e.g. by acting as co-receptor or protein binding partner [2]. Given its crucial role in insulin secretion, we investigated whether heparan sulfate modulates IL-1α activity in pancreatic islets.
Using a GAG binding assay, we observed a concentration- and sulfate-dependent binding of IL-1α to immobilized heparin but not to the non-sulfated GAG hyaluronan. Surface plasmon resonance analysis confirmed that the GAG heparin binds IL-1α with high affinity and low dissociation, indicating stable complex formation, whereas IL-1β shows almost no detectable interaction. Molecular docking of heparin (tetra- and hexa-) to IL-1α predicted two main recognition sites surrounding its N-terminal region, which displays a localized positive electrostatic potential patch. Furthermore, MD-refinement of the obtained complex structures enabled the identification of key IL-1α residues involved in heparin recognition. Competitive ELISA experiments revealed that heparin selectively enhances IL-1α binding to IL-1RI, while having no effect on IL-1 receptor accessory protein.
Immunohistochemical staining of murine and human pancreatic islets further shows the abundance of heparan sulfate at the islet surface. The enzymatic degradation of heparan sulfate via heparanase treatment increased IL-1α levels but did not affect IL-1β levels in hypoxic human islets. Removal of cell surface heparan sulfate impaired glucose-stimulated insulin secretion of islets. The heparan sulfate antagonist surfen disrupted IL-1α interactions, promoting insulin secretion in IL-1β-/- islets compared to IL-1α-/- islets.
Functionally, both IL-1α and IL-1β suppress glucose-stimulated insulin secretion in β-cells, yet heparan sulfate enhances IL-1α-mediated effects, amplifying its inhibitory impact. These findings suggest that heparan sulfate fine-tunes IL-1α but not IL-1β signaling. Targeting the IL-1α–heparan sulfate axis may offer novel therapeutic strategies to mitigate inflammation and improve islet transplantation success.

References:

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