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Exosomal microRNA: The revolutionary endogenous *Innerspace* nanotechnology

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Abstract

T lymphocytes release exosomes containing specific microRNAs that cause apoptosis of pancreatic β cells in type 1 diabetes.

Cells need to communicate efficiently with each other to coordinate functions and propagate signals. Exosomes belong to the family of extracellular vesicles: lipid membrane—bound structures actively secreted or shed from diverse cell types. Initially regarded as debris, mounting attention has focused on the theory that once released in the bloodstream, exosomes may also serve as a form of long-distance intercellular communication.

They exert key functions in recipient cells by transferring their cargos, which are different in both quantitative and qualitative terms depending on the status of the parent (exosome-producing) cell. Such bioactive cargo includes microRNAs (miRNAs), short RNA molecules that regulate gene expression via posttranscriptional degradation or translational repression. These molecules have recently emerged as ubiquitous regulators of physiological and pathophysiological processes.

Guay and colleagues demonstrated that human and rodent T cells release exosomes containing miRNAs that trigger the expression of specific cytokines and chemokines, eventually leading to pancreatic β cell death, thereby providing a novel mechanism underlying the pathophysiology of type 1 diabetes mellitus (T1DM). Although the autoimmune attack of β cells remains an established hallmark of T1DM, the exact molecular constituents of this pathway are not fully understood.

The observed exosome-mediated transfer of miRNAs from T lymphocytes to β cells had a specific cytotoxic effect on β cells without affecting insulin secretion or content; while inducing apoptosis in β cells, the exosomes released by T cells did not have any major deleterious effect on α cells, despite being internalized by both cells. One possible explanation is the miRNA-mediated activation of cell death pathways operating exclusively in insulin-secreting cells. These findings were also confirmed in human pancreatic islets. To further prove the crucial role of exosomal miRNAs in these phenomena, the authors injected a miRNA sponge in a murine model of T1DM, the nonobese diabetic mouse, to specifically inactivate noncoding RNAs overexpressed in T1DM β cells and released by activated T

cells. This treatment dramatically reduced the inflammation within islets and the incidence of the disease.

The present findings have shown for the first time that exosomal miRNAs act as key mediators of cell-to-cell communication in T1DM and that the specific inactivation of certain miRNAs prevented T1DM progression in preclinical studies. Exosomal miRNAs represent potent therapeutic targets and could also be harnessed as potential diagnostic and prognostic biomarkers.

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Highlighted Article

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