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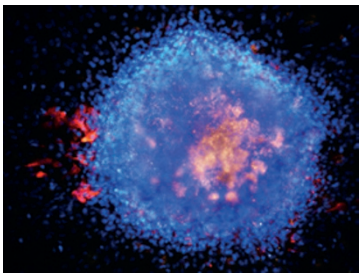
DIABETES

Enterovirus dysregulates islet miRNAs

Human pancreatic islets infected *in vitro* with coxsackievirus B5 (CVB5, a common serotype of the coxsackievirus B subtype of enterovirus B) show dysregulated expression of 33 microRNAs (miRNAs), according to new results published in *Diabetes*. Functional analysis predicts that these miRNAs target numerous risk genes for type 1 diabetes mellitus (T1DM).

"Strong epidemiological evidence and a large body of molecular data provide compelling support for the viral aetiology of T1DM," explains author Ki Wook Kim. "Many viruses … alter the function of host miRNAs and enterovirus infection disrupts the activity of multiple miRNAs in rodent pancreatic β cells." Important functions of islet β cells, such as glucose sensing, insulin release and apoptosis, are regulated by miRNAs, and Kim and colleagues hypothesized that CVB5 infection in human islets would alter miRNA expression, providing a mechanistic link between viral infection and the development of T1DM.



CVB5-infected human islets at 3 days after infection. Image courtesy of A. Alshabee-Akil.

The researchers cultured human cadaveric pancreatic islets obtained from two donors and infected the cultured cells with CVB5 or a mock-infection control. Expression of 754 different miRNAs was measured in cells harvested at three time points after infection, using high-throughput quantitative PCR nanofluidic assays.

Only two miRNAs were differentially expressed in cells from control islets and CVB5-infected islets 1 day after infection. However, by 4 days after infection, expression of 19 miRNAs was reduced in islets infected with CVB5. After 7 days, 12 miRNAs were less abundant and five miRNAs were more abundant in CVB5-infected islet cells than in control cells. In total, 33 miRNAs were dysregulated by enterovirus infection — the majority were downregulated.

Using bioinformatic software to predict gene targets, the investigators showed that the miRNAs dysregulated by CVB5 infection were predicted to regulate 57 of 72 known T1DM risk genes. "The majority of these genes were clustered as positive regulators of the innate immune response," says Kim. "Given that most of the 33 miRNAs were significantly downregulated, it is highly plausible that alteration in levels of these miRNAs will exacerbate the immune response stimulated by the virus in genetically susceptible individuals, promoting the destruction or dysfunction of β cells."

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ORIGINAL ARTICLE Kim, K. W. *et al.* Coxsackievirus B5 infection induces dysregulation of microRNAs predicted to target known type 1 diabetes risk genes in human pancreatic islets. *Diabetes* http://dx.doi.org/ 10.2337/db15-0956

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