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MicroRNA-29b Modulates Innate and Antigen-Specific Immune Responses in Mouse Models of Autoimmunity

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Abstract

In addition to important regulatory roles in gene expression through RNA interference, it has recently been shown that microRNAs display immune stimulatory effects through direct interaction with receptors of innate immunity of the Toll-like receptor family, aggravating neuronal damage and tumour growth. Yet no evidence exists on consequences of microRNA immune stimulatory actions in the context of an autoimmune disease. Using microRNA analogues, we here show that pancreatic beta cell-derived microRNA sequences induce pro-inflammatory (TNFa, IFNa, IL-12, IL-6) or suppressive (IL-10) cytokine secretion by primary mouse dendritic cells in a sequence-dependent manner. For miR-29b, immune stimulation in RAW264.7 macrophages involved the endosomal Toll-like receptor-7, independently of the canonical RNA interference pathway. In vivo, the systemic delivery of miR-29b activates CD11b+B220− myeloid and CD11b-B220+ plasmacytoid dendritic cells and induces IFNa, TNFa and IL-6 production in the serum of recipient mice. Strikingly, in a murine model of adoptive transfer of autoimmune diabetes, miR-29b reduces the cytolytic activity of transferred effector CD8+ T-cells, insulitis and disease incidence in a single standalone intervention. Endogenous miR-29b, spontaneously released from beta-cells within exosomes, stimulates TNFa secretion from spleen cells isolated from diabetes-prone NOD mice in vitro. Hence, microRNA sequences modulate innate and ongoing adaptive immune responses raising the question of their potential role in the breakdown of tolerance and opening up new applications for microRNA-based immune therapy.

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Introduction

MicroRNAs (miRNAs) are abundant, highly conserved, 18–24 nucleotides-long, non-coding RNAs. MiRNAs are known to post-transcriptionally regulate up to hundreds of genes by more or less perfect base pairing with target messenger RNAs leading to repression of translation, a process termed RNA interference (RNAi). Through RNAi, miRNAs control all fundamental biological processes like differentiation, proliferation, apoptosis, morphogenesis, inflammation, immune- and metabolic pathways [1]. MiRNAs also participate in intercellular communication after release into the extracellular space inside membrane vesicles or lipo-protein complexes that protect them against degradation. Exosomes are 40–100 nm sized membrane vesicles that transport functional mRNA, miRNAs and proteins from their cell of origin towards recipient cells [2,3]. Evidence emerges that extracellular miRNA sequences can also bind to RNA-sensing receptors of the toll-like receptor (TLR) family, independently of RNAi: in a mouse model of Alzheimer's disease, the endosomal receptor TLR-7 was identified as a key element for mir-let-7b mediated immune-stimulation exacerbating neurodegeneration [4]. Similarly, tumour-secreted miR-21 and miR-29a trigger prometastatic and inflammatory responses in macrophages through human TLR-8 or mouse TLR-7 signalling [5]. On the contrary, TLR-1 rather than TLR-7/8 seems to be involved in miRNA immune activation of natural killer (NK) cells, suggesting cell-specific pathways [6]. Whether miRNA-mediated immune-stimulation may fuel autoimmune responses has not been addressed yet.

Type 1 diabetes (T1D) is a chronic autoimmune disorder that results from the specific destruction of insulin-producing pancreatic beta cells by autoreactive T-lymphocytes, especially $CD8^+$ T-lymphocytes [7]. The mechanisms underlying the initiation and progression of the disease are poorly understood, but seem to involve the breakdown of multiple tolerance networks. To date, it is a well established fact that susceptible individuals have a complex multigenic predisposition and that environmental triggers i.e. enteroviral infections may lead to enhanced beta-cell apoptosis, dendritic cell (DC) activation and subsequent T-cell priming [8]. Immune complexes containing self nucleic acids, DNA or RNA, contribute to autoimmunity in systemic lupus erythematosus, psoriasis, polyarthritis, and diabetes [9–11]. Aberrant miRNA expression patterns have been associated with disease progression in T1D patients [12,13]. Whether miRNA missexpression is merely a consequence of T1D or whether miRNAs participate in disease development remains to be investigated.