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A brief glimpse over the horizon for type 1 diabetes nanotherapeutics

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Abstract The pace at which nanotherapeutic technology for human disease is evolving has accelerated exponentially over the past five years. Most of the technology is centered on drug delivery which, in some instances, offers tunable control of drug release. Emerging technologies have resulted in improvements in tissue and cell targeting while others are at the initial stages of pairing drug release and drug release kinetics with microenvironmental stimuli or changes in homeostasis. Nanotherapeutics has only recently been adopted for consideration as a prophylaxis/treatment approach in autoimmunity. Herein, we summarize the current state-of-the art of nanotherapeutics specifically for type 1 diabetes mellitus and offer our view over the horizon of where we envisage this modality evolving towards.

1. Introduction

Nanoparticles (NPs) are conventionally-described as objects with a diameter less than 100 nm. Due to their small size and surface area they can exhibit unique electronic, optical and magnetic properties that can be applied to biomedicine [1–3]. When considered *in toto*, the different variations of NP formulations actually constitutes a very heterogeneous group that is somewhat challenging to classify into specific categories. Nevertheless, one can being by classifying NPs based on the physico-chemical properties, loading potential, route of administration, biodistribution properties, potential for toxicity, primary particle size, agglomeration/aggregation state, size distribution shape, crystal structure, chemical composition, surface chemistry, surface charge and porosity [1–7]. Even this exhaustive categorization cannot account for all the potential properties of NPs that can provide distinguishing features offering specific biologic activities that would better serve one therapeutic target over others.

When considering the very basic NP applicability, drug delivery is often the first therapeutic approach that comes to mind. Indeed, as shown in Table 1, a number of NP formulations are under development to deliver immunomodulatory agents for a variety of immune-mediated conditions, especially those where the objective is to suppress the immune system and attenuate inflammation. This review will not focus on the translation of such approaches to treating type 1 diabetes mellitus (T1DM) given the self-evident application of the

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Table 1 NP: load of potential utility in treating T1DM.

Carrier	Load/modification	Reference(s)
PLGA	Cyclosporin A	[107]
	Rapamycin	[108,109]
	Tacrolimus	
	siRNA/antisense to CD40	[110–112]
	Autoantigens	[113,114]
	CD4-targeting LIF load	[115]
	MARCO	[113,114]
	CCL22	[116]
	Rapamycin, IL-2, and TGF-beta	[117]
	Vitamin D3/TGF-beta/autoantigens	(Lewis et al. this issue)
	DEC-205 targeting	[118,119]
MPEG-PLA	Tacrolimus	[120]
Liposomes	Glucocorticoids	[121]
	CD22-targeting ligands	[122]
	Tacrolimus/rapamycin	[45]
	Mannose receptor/CD206-targeted	[123,124]
Dendrimers	Methotrexate	[125]
	Azabisphosphonate	[126]
PLL-PEG	Oligonucleotides (antisense to CD40, CD80, CD86)	[54]
	siRNA to CCR2	[127]
Iron oxide	pMHC-coupled/autoantigens/toxin-coupled NPs	[55,128,129]
Magnetic NPs	Beta-2 microglobulin/caspase-3 siRNA	[127]
AuNPs	Autoantigen/AhR ligand	[130]
Cyclodextrin gels	MMF	[131]

technologies listed in Table 1 to preventing and treating T1DM. Instead, we propose to summarize and discuss what we consider as novel and innovative approaches to deliver drugs, modulate cell accumulation into sites where biologic modification is sought, target drugs in a tissue- and cell-specific manner and possibly use changes in microenvironmental homeostasis as triggers for drug release and cell activity modulation.

2. The immune system and nanoparticles

Autoimmune diseases like rheumatoid arthritis (RA), multiple sclerosis (MS), and T1DM are the third ranked cause of human morbidity and mortality in United States [8–10]. Allergies including allergic asthma and severe food allergies affect ~20% of the population while the prevalence of autoimmune diseases in the general population is currently at 4.5% [11–17]. The standard-of-care as well as emerging therapies are centered on systemic delivery of immunosuppresive drugs that require chronic administration which can exacerbate opportunistic infections, reactivate latent pathogens and can predispose to malignancy [18–33]. Emerging data indicate that other than targeting the specific effector cells involved in the actual tissue damage, it may be more attractive and easier, to target a therapeutic to the site(s) where immune cells acquire the ability to become effector cells (those that actually physically cause the damage, either by cytokines or by direct killing). In almost all instances, these sites are the lymphoid organs, and more specifically, the lymph nodes draining the tissues that are targeted for immune-mediated impairment and damage [34–43]. While intranodal cell and drug delivery is not particularly novel, it may be better to administer sustained-release, or tunable-release NP formulation of drugs and agents listed in Table 1. We show the concept in Fig. 1. The question is what type of delivery approach is best and to what cell type can these NPs be delivered to? Equally, if not more relevant, is how can one deliver such NPs to lymph nodes that are apposed to the internal organs? One potential answer lies in a comprehensive understanding and mapping of the lymphatic fields draining into a desired lymph node.

3. Delivery: systemic or site-directed?

While systemic delivery of NP is the easiest in terms of procedure, and may be the most effective in other disease states and pathologies, it is not the best suited for targeting organs other than spleen, liver, lungs, and kidneys. Indeed, depending on the payload, systemic effects may mask the potential benefits, or even confer adverse events. In contrast, a significant mass of data clearly point to the pancreas and the pancreatic lymph nodes as the most desired tissues in which it is possible to modulate the autoimmunity underlying T1DM [34–38].

In general terms, the lymphatic system constantly drains fluid and macromolecules from interstitial space, creating small interstitial flows on the orders of 0.1–1 μm/s. By designing NPs that are in that size range they can be transported to interstitial flow through the interstitial matrix into the draining lymphatic capillary beds [44]. Following subcutaneous administration, NPs less than 100 nm diameter are taken up by lymphatic capillaries and migrate/accumulate inside the draining lymph nodes (LNs). The LNs are the major depots of immune cells like T-cells and DC