

Chapter 2

Drug Delivery Strategies for Tolerogenic Therapy for Autoimmune Diseases in an Antigen-Specific Manner

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ABSTRACT

Autoimmune diseases are the result of an improper immune response towards a self-antigen. Predominantly, autoimmune diseases have been treated using therapies that suppress systemic immune responses, which can result in significant side-effects like increased risk of infection and cancer. Alternatively, induction of immune tolerance through antigen-specific therapies can inhibit disease-associated responses without systemic suppression. Previously, immune tolerance has been accomplished by soluble antigen delivery through oral, nasal or sublingual routes. However, these therapies have shown minimal success in clinical settings. In an attempt to increase the efficacy of these therapies, recent work has utilized microparticulate delivery vehicles for the induction of immune tolerance. Microparticles are capable of increasing the solubility and circulation of cargo. In addition, their ability to passively target macrophages and dendritic cells increases their capacity for modulating the immune response. Recent work has shown microparticles fabricated with disease-associated antigens have limited disease progression and severity in animal models of Multiple Sclerosis, Type 1 Diabetes and Rheumatoid Arthritis. Inhibition of disease progression has corresponded with an antigen-specific decrease in inflammatory responses. The emerging field of inducing tolerance through microparticle-based therapies can limit therapeutic side-effects and increase patient quality of life by providing for long-term suppression of autoimmune disorders without compromising systemic immune function.

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INTRODUCTION

Autoimmune Diseases

According to the National Institutes of Health (NIH), approximately 23.5 million Americans are living with at least one autoimmune disease. These diseases, which can occur in almost any tissue, are the result of an improper immune response towards self-antigens. In some cases, such as systemic lupus erythematosus (SLE), the immune response mounts a response that targets multiple healthy tissues, while others like Multiple Sclerosis (MS), Type-1 Diabetes (T1D) or Rheumatoid Arthritis (RA) are more organ or site specific. Current therapeutic strategies for autoimmune diseases provide amelioration of symptoms, most commonly through systemic immune suppression, but fail to treat the underlying causes of disease. Although autoimmune diseases manifest themselves very differently, a number of current therapeutics have similar strategies for immune suppression, including inhibition of T cells, B cells, and pro-inflammatory cytokines. This chapter will discuss a number of therapeutic approaches for common autoimmune diseases, as well as the emerging field of nano/microparticulate therapeutics for the treatment of autoimmune diseases.

Multiple Sclerosis

MS is a chronic demyelinating disease of the central nervous system (CNS) and affects nearly 2.5 million people worldwide, at a yearly cost burden of up to \$54,000 per patient (Adelman, Rane, & Villa, 2013). T cells targeting auto-antigens in the CNS is believed to be the initial step that drives pathogenesis of MS (Friese, Schattling, & Fugger, 2014). Although the exact mechanism is not clearly known yet, the focal areas of demyelination in the white matter (plaques) are seen as the first site of attack. Immune cells (such as T cells and macrophages) invade across the blood–brain barrier, which further promotes inflammatory responses in the brain parenchyma, leading to demyelination and axonal degeneration (Smith & McDonald, 1999). Current therapies for MS have been successful at decreasing disease symptoms through a wide variety of immunomodulatory, antibody, or small molecule therapies. Interferon beta (IFN- β) (Avonex, Betaseron, Extavia, or Rebif) and glatiramer acetate (GA) (Copaxone) are frontline immunomodulatory therapies for the treatment of MS. IFN- β is a protein that was the first therapy to be accepted for use against MS. This injectable has shown to be effective at decreasing relapse rates, as well as slowing progressive forms of MS. Despite the wide usage of IFN- β , its specific mechanism is yet to be fully understood, though it has been associated with the inhibition of leukocyte migration, decreased inflammatory cytokines, and inhibition of T cell survival and expansion (Dhib-Jalbut & Marks, 2010). It is likely that a combination of these immunomodulatory properties is what makes IFN- β effective for some MS patients. However, a clinical study on IFN- β showed a large number of patients stopped low-dose therapy due to poor efficacy, while the most common causes of stopping high-dose therapy were adverse events, like flu-like symptoms (Ruggieri et al., 2003). Due to these drawbacks, alternative therapies are necessary for a large number of patients. GA is seen as a viable alternative to IFN- β (Vallittu et al., 2005). GA is a daily sub-cutaneous injectable that is a random sequence of four synthetic polypeptides resembling myelin protein. It is thought to be effective against MS by dampening pro-inflammatory responses in the brain, outcompeting endogenous myelin for antigen presentation by antigen presenting cells (APCs), and suppressing responses towards other myelin-associated antigens (Ziemssen & Schrempf, 2007). Though the exact mechanism has yet to be elucidated, GA has been a

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