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Glatiramer acetate and therapeutic peptide vaccines for multiple sclerosis

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Abstract

Therapeutic vaccines are antigen-specific agents that inhibit an unwanted immune response to prevent progression of, or eliminate, existing disease. Unlike prophylactic vaccines, developing therapeutic vaccines poses a significant challenge because they can require multimodal immunomodulatory activity to modulate complex pathogenic disease pathways. This is particularly true in autoimmune disorders, including multiple sclerosis, which has complex pathogenesis that, although not fully understood, appears to involve dysfunction of both innate and adaptive immune processes. The glatiramoid, glatiramer acetate (Copaxone®), a nonbiologic, complex, heterogenous mixture of synthetic polypeptides, is currently the only approved therapeutic peptide for treatment of multiple sclerosis. Glatiramer acetate has an enormous number of potentially active epitopes (estimated to be $\sim 10^{30}$) in the polypeptides mixture. The epitopes in glatiramer acetate have not been identified, but they appear to act as altered peptide ligands of encephalitogenic epitopes within myelin basic protein, a suspected autoantigen implicated in multiple sclerosis. Peptide epitopes in glatiramer acetate compete with autoantigens for binding with major histocompatability complex molecules on antigen-presenting cells, thereby altering the functional outcome of T cell signaling from inflammatory to anti-inflammatory responses. Other therapeutic vaccines designed to more selectively compete with myelin antigens for receptor binding have been shown effective in animal models of multiple sclerosis but toxic in human patients in clinical trials. The partially random structure of glatiramer acetate and potentially huge number of antigenic sequences may be integral to safety and efficacy by influencing multifactorial immune processes and surmounting challenges related to inter- and intra-individual heterogeneity of T cell responses and the phenomenon of epitope spreading. Follow-on generic versions of glatiramer acetate have been made available to multiple sclerosis patients outside the United States. Analyses of these glatiramoids indicate they have different biological and immunological activity from that of Copaxone®, illustrating the difficulty of replicating complex glatiramoids and of developing safe, effective peptide vaccines in general. Reviewed here are some of the major mechanisms of glatiramer acetate activity on innate and adaptive immune pathology and considerations for development of future therapeutic peptide vaccines for multiple sclerosis.

keywords: Autoimmune disease, glatiramer acetate, glatiramoid, multiple sclerosis, peptide, copolymer, therapeutic, vaccine

Introduction

Most vaccines are used for prophylaxis of disease; however, therapeutic vaccination involves the use of an antigen-specific intervention to inhibit an unwanted immune response, with the goal of preventing progression of, or eliminating, existing disease [1]. Effective therapeutic vaccines are less common than preventive vaccines and are more challenging to develop because preventive vaccines typically have immunologic specificity for an individual infective agent (e.g., viral poliomyelitis, smallpox). In contrast, therapeutic vaccines may require multimodal immunomodulatory activity to modulate complex pathogenic disease mechanisms already underway. Suppression of harmful inflammatory immune responses by antigenic peptide vaccination requires induction of tolerance, which can be attained by repeated dosing [2].

There is great interest in developing therapeutic peptide vaccines for treatment of autoimmune diseases such as multiple sclerosis (MS) [3-8]. Synthetic peptides, in principle, could be

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designed to present selected epitopes to immune cells to elicit a desired response. MS is a chronic, progressive, neurodegenerative autoimmune disease of the central nervous system (CNS) associated with demyelination and axonal damage. MS is a disease with no identified specific pathogenic target for prophylaxis. The etiology of MS is unknown, and pathogenesis is complex and not fully understood, but appears to include pathologic mechanisms of innate and adaptive immunity working together to exacerbate disease (**Figure 1**) [**9**-**11**]. Therefore, an effective vaccine will optimally modulate both innate and adaptive immune responses. Currently, the glatiramoid, glatiramer acetate (GA, Copaxone®), a non-biologic complex drug (NBCD), is the first and only approved therapeutic peptide for treatment of MS [**1**,**2**,**12**]. Copaxone® and the interferon beta (IFNβ) drugs (protein products produced by recombinant DNA techniques, including Avonex®, Rebif®, and Betaseron®) were the first disease-modifying therapies (DMTs) approved for treatment of MS. The IFNβ drugs have profound activities on several components of the process required for the migration of inflammatory cells into the CNS. These agents have been shown to reduce relapse rate, delay progression of neurologic disability, and decrease brain lesions on MRI in patients with relapsing-remitting MS (RRMS) [**13**-**16**]. Unlike GA activity (described below), a primary mechanism of the IFNβ drugs is reduction of inflammatory cell trafficking into the CNS [**10**,**15**,**16**]. More recently, several oral MS treatments have become available, including Aubagio® (teriflunomide), Tecfidera® (dimethyl fumarate), and Gilenya® (fingolimod).

That GA is the only therapeutic peptide approved for MS reflects the complexity of the disease and of GA, and the challenges of preparing safe and effective therapeutic peptide vaccines. Reviewed here are some of the key mechanisms of GA activity on innate and adaptive immunity that contribute to its efficacy and safety, and considerations for development of follow-on versions of GA and new peptide vaccines for MS.

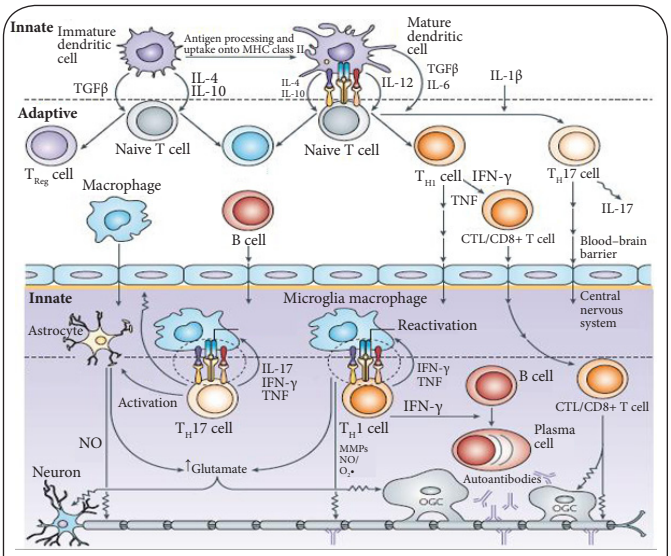

Figure 1. Multiple sclerosis pathogenesis involves innate and adaptive immune dysfunction. Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Drug Discov. Nov;9(11):883-97, copyright 2010 [**115**].

Review

Glatiramer acetate

Discovery

The immunomodulatory benefits of GA were discovered serendipitously. In the 1970s, researchers at the Weizmann Institute in Israel synthesized a series of amino acid copolymers in hopes of developing synthetic antigens that mimic myelin basic protein (MBP), the main protein component of the lipid-rich myelin sheath and a major autoantigen in MS. The copolymers were designed to reproducibly induce experimental autoimmune encephalomyelitis (EAE), an animal model of MS. However, rather than induce EAE, GA immunization proved to be protective against EAE induction and reduced symptoms of established EAE in several animal species [**17**-**20**].

Chemical nature

GA is a complex, heterogenous, partially random mixture of synthetic polypeptides containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-lysine, and L-tyrosine [**21**]. The polypeptides chains in GA vary in length from 20 to 200 amino acid residues, with an average of approximately 60 residues, and molecules in the colloidal GA sus-pension range in size from 1.5 nm to 550 nm, making GA one of the first true nanomedicines [**22**,**23**]. The average molecular weight of the polypeptides in GA is 7000-9000 daltons. GA has an enormous number of potentially active epitopes (estimated to be ~10^{30} [**24**]) in the polypeptides mixture, which may be integral to drug efficacy and safety [**25**]. However, the complexity of GA makes isolation and identification of the active epitopes in the GA polypeptides mixture impossible. Nevertheless, it is possible to differentiate among glatiramoids (i.e., synthetic copolymer mixtures comprising the four amino acids in GA in a defined molar ratio [**22**]) in analytical and biological tests (as described below).

Clinical usage

Copaxone® is indicated for the treatment of patients with relapsing forms of MS [**21**]. Copaxone® is currently available as a daily 20 mg SC injection (approved in the US in 1996) and recently approved in the US in January 2014 as a 40 mg SC injection administered three times per week.

GA mechanisms of action

Numerous effects of GA on cellular and humoral immune cells have been identified over the last 4 decades, though the complete activity of GA remains unknown and new mechanisms continue to be discovered (**Figure 2**) [**22**,**25**,**26**]. Perhaps the best-known therapeutic mechanisms of GA activity involve its effect on adaptive immune cells (T and

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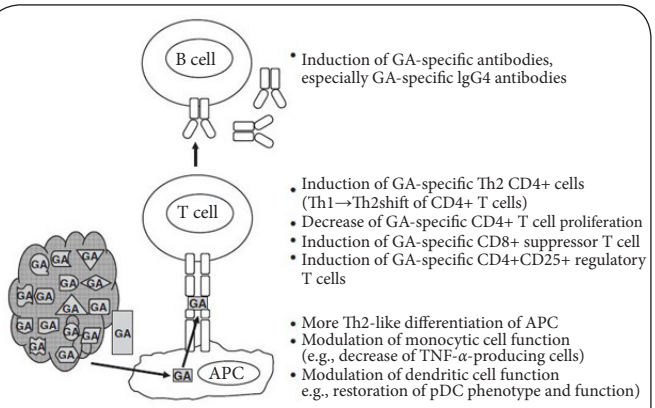

Figure 2. Glatiramer acetate modulates innate and adaptive immune cells. Reprinted from Int Rev Neurobiol Vol. 79, Ziemssen and Schrempf, Glatiramer acetate: mechanisms of action in multiple sclerosis, pp. 537-570 (2007), with permission from Elsevier [20].

B lymphocytes). More recently, GA effects on cells of the innate immune system (e.g., antigen-presenting cells [APCs], natural killer [NK] cells) have been discovered.

GA effects on innate immune cells

Antigen-presenting cells: The main functions of APCs are phagocytosis, antigen presentation, and cytokine production. In the peripheral immune compartment, APCs provide three sequential signals to activate antigen-specific T cells:

1) Toll-like receptors (TLRs) on activated APCs recognize bacteria, viruses, and other antigens [27,28]. Upon phagocytosis, antigenic peptide fragments bound to major histocompatibility complex (MHC) molecules on the surface of APCs facilitate T cell recognition of the cognate antigen by T cell receptors (TCR) on CD4+ cells (antigen presentation on MHC class II molecules) or CD8+ cytotoxic T cells (antigen presentation by MHC class I molecules);
2) Costimulatory molecules on APCs activate the T cells to initiate proliferation and differentiation; and
3) Cytokine secretion by APCs polarizes differentiation of activated CD4+ T cells into different effector (T helper Th; e.g., Th1, Th2, Th3, Th17) and regulatory (e.g., CD4+CD25+FoxP3+) T cell subtypes; influences cytotoxic CD8+ T cell phenotypes [29]; and instructs plasma cell differentiation.

In MS, peptide epitopes from putative MS autoantigens, including MBP, myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP) molecules, bind to MHC class II molecules on APCs. Upon T cell recognition, pro-inflammatory (Type I) cytokines are expressed and stimulate differentiation and proliferation of pathogenic autoreactive CD4+ Th1 cells [10,30]. Reciprocally, APCs exposed to pro-inflammatory T cells *in vitro* tend to express a range of adhesion molecules, costimulatory molecules, and cytokines favoring further T cell differentiation of pro-inflammatory Th1 cells. Activated myelin-reactive Th1 cells in the periphery move from the systemic circulation across the blood-brain barrier (BBB) and enter the CNS [12]. Once Th1 cells establish an inflammatory milieu there, pro-inflammatory Th17 cells can enter the CNS [31]. Th17 cells play an important role in the pathogenesis of inflammatory and autoimmune diseases [32]. Once in the CNS, antigenic peptide fragments bound to dendritic cells (DCs), microglia, and astrocytes reactivate autoreactive T cells, leading to pro-inflammatory cytokine release and myelin damage.

Circulating APCs of the myelomonocytic lineage, i.e., monocytes/macrophages, and DCs, may be the primary targets of GA immunomodulation. GA activity on monocytes, DCs, and microglia is antigen-nonspecific, which may help explain why GA has shown efficacy in animal models of several inflammatory and neurodegenerative conditions [33-39].

GA polypeptides are promiscuous binders to MHC class II molecules on APCs, with or without antigen processing [40]. GA peptides compete with myelin peptides for binding to MHC class II molecules on APCs and can preferentially displace peptides from MBP [41], MOG [42], and PLP [43] from the MHC binding site, but cannot be displaced by them [44]. As a result, differentiation of autoaggressive Th1 cells is reduced and GA mediates a shift in T cell phenotypes from Th1 to Th2/3 cells.

Monocytes cultured in anti-inflammatory supernatants push T cells toward Th2 differentiation *in vitro*, which is associated with secretion of anti-inflammatory (Type II) cytokines [45]. GA induces Type II monocyte and microglia differentiation in EAE models and in MS patients [45-48]. Adoptive transfer of monocytes from GA-treated mice to GA-naïve mice with EAE directs T cell differentiation toward Th2 cells and CD4+CD25+FoxP3+ Tregs, an important subclass of regulatory cells that attenuate autoreactive T cell responses [47].

Continued GA treatment reduces the ability of APCs to present antigen or to respond to various stimuli [45-49]. In mice with EAE, GA reduced expression of TLRs on DCs [50], and down-regulated osteopontin, a protein implicated in chronic inflammatory diseases that induces DC maturation toward the Type I inflammatory phenotype. In another study, GA inhibited monocyte activation and production of pro-inflammatory tumor necrosis factor alpha (TNFα) by human DCs *in vitro* [48], and compared with untreated patients, DCs and monocytes from MS patients who received GA for 1 year showed less activation, accompanied by reduced risk of relapse [51].

The ability of APCs to penetrate the BBB is essential to the establishment of autoimmune inflammatory CNS diseases. Suppressed expression of chemokines with CNS chemotactic properties may also contribute to GA therapeutic activity [50]. Macrophage inflammatory protein (MIP)-1 increases DC transmigration across endothelial cells and is elevated in mice with EAE compared with control mice. Daily GA treatment suppressed MIP-1α and MIP-1β expression in mice with EAE, and also decreased expression of RANTES [50,52], a poly-

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peptide with strong chemoattractant activity for T cells, monocytes and macrophages associated with pathogenesis of MS lesions in the CNS [52].

Attesting to the primacy of GA effects on APCs, researchers showed that GA did not influence T cell polarization when added to naïve Th cells activated in an APC-free system. Moreover, induction of Type II monocytes by GA does not require reciprocal signalling by T cells, [53]. In STAT6-deficient mice, which cannot generate interleukin (IL)-4-producing Th2 cells, monocytes from GA-treated mice exhibited increased Type II anti-inflammatory cytokines, IL-10, and transforming growth factor beta (TGFβ) [47]. Similarly, monocytes from GA-treated RAG-1 mice, which lack mature T and B cells, also showed an anti-inflammatory cytokine pattern [47].

Natural killer cells: NK cells are lymphocytes of the innate immune system responsible for immunosurveillance and regulating immune responses [54]. NK cells limit damage in MS by inhibiting autoreactive T cell responses, and increased frequency or functional competence of circulating NK cells is associated with decreased disease activity in MS patients [55]. NK cells exposed to GA kill both immature and mature DCs, impairing the ability of mature DCs to present antigens to autoreactive T cells [54,56,57]. This mechanism may be involved in GA effects on inhibiting graft-vs-host (GvH) disease in laboratory animals [36,58].

GA effect on adaptive immune cells

CD4+ T cells: Therapeutic effects of GA have been attributed in part to the ability of antigenic sequences in hydrolyzed GA peptides to act as altered peptide ligands (APLs) of encephalitogenic epitopes in MBP [1,12,59,60]. An APL serves as a receptor ligand that contains a substitute of one or more amino acids of the native ligand to change the functional outcome of TCR signaling [61]. An APL must be close enough in chemical composition to the native peptide antigen to trigger an immune response that is cross-reactive with the infectious agent or autoantigen, but must itself be biologically harmless. Accordingly, GA is cross-reactive with myelin antigens at both the humoral and cellular levels, without being encephalitogenic [62-67]. Repeated GA immunization modifies the GA-reactive T cell repertoire by skewing them from the Th1 phenotype toward the Th2 phenotype [59,66,68,69]. GA-reactive Th2 cells release anti-inflammatory cytokines and neurotrophic factors [69-71] and suppress neighboring auto-aggressive Th1 cells by means of "bystander suppression" in the CNS [68,69]. GA treatment also increases the number and suppressive capacity of CD4+CD25+FoxP3+ Tregs in MS patients [72,73]. Tregs dampen autoimmune responses, and are functionally impaired in MS patients [74].

CD8+ T cells: Untreated patients with MS initially show low GA-specific CD8+ cell responses compared with healthy controls [75], but GA therapy produces proliferative responses in CD8+ T cells [75,76]. Adoptive transfer of GA-induced CD8+ T cells results in amelioration of EAE [77]. GA-reactive CD8+ T cells appear to regulate proliferation of myelin-reactive CD4+ cells [75,78]. Over time, continued treatment with GA results in decreasing numbers of GA-reactive CD4+ T cells while the number of GA-reactive CD8+ T cells increases [79]. It has been proposed that GA effects on CD8+ T cells may be an indispensable component of its therapeutic activity [77].

B cells: B cells can serve as efficient APCs for T cells and can activate autoreactive T cells; likewise, activated T cells can trigger B cell activation and formation of autoreactive antibodies [12,80]. Demyelinating antibodies can travel from the systemic circulation across the BBB and into the CNS. Antibody-mediated patterns of demyelination are detected in more than 50% of MS patients [81].

All patients treated with GA develop GA-reactive antibodies [67,82]. As an antigen-based therapy, by definition anti-GA antibodies are not neutralizing and do not appear to interfere with MHC class II binding or induction and proliferation of suppressor T cell lines and clones [82]. GA treatment produces B cell secretion of the Type II cytokine, IL-10, thereby augmenting suppression of autoreactive T cells, and promoting induction of GA-reactive Th2 cells [83]. GA effects on B cells may also be essential to therapeutic activity. Adoptive transfer of B cells from GA-treated mice with active EAE inhibited the proliferation of autoreactive T cells, whereas GA treatment had no effect on EAE in B cell-deficient mice [84]. In a clinical study, relapse-free patients tended to develop higher anti-GA antibody titers than patients who relapsed [67], suggesting beneficial antibody activity. Additionally, remyelination of spinal cord axons was promoted by antibodies to GA in mice with EAE [85].

Anti-GA antibody levels peak between 3 and 6 months of treatment initiation, and then gradually decline, but remain higher than baseline levels [67,82]. Anti-GA antibodies are mainly immunoglobulin G1 (IgG1), IgG2, IgG4, and IgA isotypes [67,82,86,87]. IgG1 antibody levels remain relatively consistent over time. IgG2 antibodies decline with chronic treatment [86] and a gradual shift to IgG1 and IgG4 is observed [87]. GA was not cross-reactive with MBP when exposed to polyclonal antibodies, but cross-reactivity with MBP was evident with monoclonal antibodies, *in vitro* [63]. RRMS patients in clinical trials developed GA-reactive antibodies with very low reactivity to MBP [67,82].

Selective peptide vaccine attempts

Given the APL activity of the random GA mixture, selective APLs were developed with the intent of creating more potent inhibition of autoreactivity. Two APLs of the immunodominant peptide region (83–99) of MBP (alanine was substituted for lysine at position 91 in both cases) were developed for use as therapeutic vaccination for MS. While effective for preventing and treating EAE in laboratory animals, they were less successful for MS patients, primarily due to toxicity problems [88,89]. The selective APL, NBI 5788, was evaluated in MS patients randomized to receive once-weekly SC injections

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of doses ranging from 5 to 50 mg for up to 4 months in a phase II clinical trial [88]. The study was stopped prematurely when 9% of patients developed immediate-type hypersensitivity reactions. There was a robust Th2-like immune response in NBI 5788-treated patients. Th2 cell responses are associated with the promotion of humoral responses, and anti-NBI 5788 antibody titers were relatively high in patients with hypersensitivity reactions, particularly in patients who received the highest tested dose. Thus, the strength of the Th2 response is an essential consideration in peptide vaccine design; i.e., optimization of the suppression of Th1-related autoimmunity must be balanced against the risk of hypersensitivity reactions driven by Th2 responses [88].

Weekly administration of the APL, CGP77116, was assessedin another small phase II study [89]. Of 8 patients treated with CGP77116, 2 showed improved disease activity, 3 had stable disease, and 3 showed worsened disease activity during and immediately after treatment. CGP77116 was poorly tolerated and the trial was discontinued before completion. An investigation showed activated CGP77116-reactive T cells skewed toward the inflammatory Th1 phenotype rather than Th2, and on-study relapses were ascribed to CGP77116-induced expansion of encephalitogenic T cells specific for $MBP_{(83–99)}$ [89].

Based on these studies, it was suggested that when relying on TCR- or MHC-mediated therapeutic effects (i.e., MHC blockade, TCR antagonism or partial agonism, clonal deletion or anergy), a single selected APL will be ineffective across individuals with different genetic backgrounds, and even intra-individually because TCR diversity may preclude a consistent therapeutic response [61]. Humans may express up to 8 different class II alleles; consequently, there is considerable diversity in the number of different antigenic peptides that can be presented to T cells among different individuals [61]. Varying autoantigens may be important in different individuals and phenotypic T cell response to an antigen may be heterogeneous. Further, by the time MS becomes clinically evident in humans, it is likely that the immune response has spread to more than one antigen due to "epitope spreading" [61]. Thus, adverse effects seen with NBI 5788 and CGP77116 were likely related to the many clonotypes that exist within and among different patients against the targeted epitope, $MBP_{(83-99)}$ [90].

Immune dysregulation at multiple levels appears to cause MS, and this may explain an observed resistance to therapeutic modalities with high immune selectivity. GA is a pool of antigenic peptides of different lengths and composition with complex partially random structure and potentially millions of antigenic peptides [24,25]. An antigenic epitope in GA for a distinct TCR would be present at much lower concentration than if the GA structure were defined and not random [61]. GA administration is thought to lead to anergy of T cells for which TCR-binding motifs in GA occur with higher frequency and to persistence or expansion of T cells with TCR-binding motifs in GA that occur with low frequency [61]. With GA, this implies the induction of anergy for Th1/Th0 GA-specific T cells and persistence/expansion of Th2 GA-specific T cells.

Follow-on glatiramoids-special considerations

The challenge of creating peptide vaccines is exemplified by attempts to create follow-on versions of Copaxone®. GA and other NBCDs are heterogenous mixtures of closely related, macromolecular, nanoparticulate components that cannot be entirely characterized physicochemically using available analytical technology [91]. The consistent activity and the quality of NBCDs rely on strictly controlled, proprietary manufacturing procedures [91-93]. Even small variations to the manufacturing method or of ingredient quality used to synthesize GA can increase the risk of safety problems or of reduced therapeutic efficacy [94-96]. While Copaxone® is not encephalitogenic and does not induce autoreactive antibodies, the same cannot be assumed for a follow-on GA-like product.

Several purported "generic" GA products have been marketed in countries outside of the United States (US), and generic GA products await US FDA approval at this writing [97,98]. While it is not possible to show that a generic product is the same as Copaxone®, demonstration of "similarity" may be adequate for generic approval. Thus far, comparisons of physicochemical and biological activity have shown differences between purported generic GA products and Copaxone® [99,100]. A purported generic GA product is currently marketed in India (Glatimer®, Natco Pharma, Ltd., Hyderabad, India) [99]. No information about the safety, efficacy, or immunogenicity of this product in RRMS patients has been published at this time. However, in analytical tests, Glatimer® has demonstrated physicochemical differences from GA [95,96], and gene expression studies, which provide a "snapshot" of biological processes stimulated by glatiramoid treatment, show Glatimer® also has different biologic activities from those of GA [99,100]. In 2 separate studies, activated splenocytes from GA-treated mice showed distinctly different gene transcription profiles when reactivated *ex vivo* by Glatimer® or GA [99,100]. As previously described, among GA effects on APCs is down-regulation of macrophage and monocyte activation, and among GA effects on T cells is skewing T cell differentiation toward a Treg phenotype that limits autoimmune activity [73,101]. **Figure 3** shows the relative expression of Treg-specific, macrophage-specific, and monocyte-specific genes in splenocyte samples reactivated by GA compared with samples activated by Glatimer® [100]. A cell-type enrichment algorithm showed the gene expression profile produced by splenocytes activated with Glatimer® was significantly enriched in genes associated with macrophages and monocytes compared with the gene expression profile of splenocytes activated by GA. Similarly, compared with GA, the list of genes down-regulated by splenocyte activation with Glatimer® was significantly enriched in genes associated with Tregs. Thus, Glatimer® could have very different immunomodulatory effects than GA. Another important finding of gene expression studies was poor batch-to-batch reproducibility among Glatimer® batches (**Figure 4**) [99,100].

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