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Immune modulation and possible pathological implications mediated by naturally produced immunoglobulin G idiotypes: from historical to recent experimental and clinical studies focused on atopic dermatitis

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Since the 1950s decade, it has been suggested that a naturally produced or induced repertoire of immunoglobulin G (IgG) idiotypes may exert some immunoregulatory functions. In the last decades, some more advanced theories have suggested that the repertoire of IgG idiotypes may influence the development or control of some atopic diseases. In atopic dermatitis (AD), some evidence indicated that the IgG repertoire obtained from these patients could effectively mediate regulatory functions on thymic and peripheral CD4+ and CD8+ T cells. Furthermore, some recent clinical trials have corroborated the hypothesis that IgG from AD patients can exert regulatory functions *in vivo*. Here, we revised some historical aspects that yield current approaches developed *in vitro* and *in vivo* to elucidate a recently proposed theory termed "hooks without bait" that can strengthen the broad spectrum of research about evaluating different sets of IgG idiotypes and determine their immunological effects.

Keywords: Immunoglobulin G, Idiotypes, Anti-idiotypic antibodies, Atopic dermatitis, CD4+ T, CD8+ T

Introduction

In 1955, Jerne [1] proposed the natural-selection theory of antibody formation, on which it was suggested that humans can spontaneously produce antibodies with an affinity toward any antigen to which the animal can respond. This theory significantly expanded the perception of immunological interactions mediated by human antibodies and started discussions on possible interactions between antibodies' naturally produced idiotypes (specificities) with B and T cells clonal receptors (BCRs and TCRs).

Later, in 1974, the same scientist (Niels Kaj Jerne) proposed the network theory of the immune system, where the idiotype recognition by a secondary anti-idiotype antibody (anti-Id) that mimics the antigen's structure could inhibit the recognition of an antigen by the primary antibody [2]. In collaboration with other scientists, a set of theories by Jerne [3] resulted in the award of the Nobel Prize in 1984. After being awarded, this author revisited its theory in a manuscript where some additional functions were suggested

for anti-Id recognition [3]. One year later, Jerne [4] stated that the immune system of an animal produces specific antibodies to an antigen and antibodies that recognize the idiotypes it has made, revealing the tremendous immunological magnitude and relevance of anti-Id interactions. In parallel, the 1980s decade was characterized by the consolidation of the scientific knowledge about the recognition of TCRs by anti-Id antibodies due to a set of highly qualified studies that had experimentally demonstrated these interactions [5-7], including the original demonstration that anti-Id antibodies could induce specific T cell immunity [8]. Since then, the requirement for studies to investigate autologous interactions between TCRs and antibodies has become evident. Similarly, some pivotal observations on BCRs were obtained in the 1980s, demonstrating that the early appearance of multiple idiotypes depends on anti-Id antibody interactions and that the interference with these interactions may influence adult B cell repertoire [9].

In 1994, Marchalonis et al. [10] first demonstrated that naturally produced human antibodies could directly recognize TCRs' variable domain and constant region determinants. In the same study, it was demonstrated that the levels of natural antibodies against the variable domains of TCRs tend to be higher in rheumatoid arthritis patients than in healthy individuals or systemic lupus erythematosus patients, suggesting that the recognition of TCRs by anti-Id antibodies may participate on natural immune regulation. Furthermore, it was demonstrated in 1996 that the level of a circulating idiotype regulates the production of the complementary anti-Id antibody, which corroborates with the hypothesis of an integrated regulation involving recognizing TCRs and BCRs that can potentially influence the development of several immune responses [11].

Several studies were developed from these observations, and in 2003, it was evidenced that polyclonal immunoglobulin G (IgG) immunoglobulin preparations used for human therapeutic purposes (intravenous immunoglobulin, IVIg) contain anti-Id antibodies that can recognize variable domains of TCRs and that these antibodies can at least in part, mediate the immunomodulatory effects observed in T cells [12].

In 2007, it was proposed that the immune system may compensate for the manifestation of inflammatory diseases, primarily autoimmune, by naturally producing immunomodulatory anti-Id antibodies [13]. This study experimentally demonstrated that autoantibodies against TCR Vbeta chains could inhibit T helper type 1 (Th1)-mediated inflammatory reactions, a valuable and unprecedented observation. A few years later, it was also shown that IVIg could spontaneously interact with BCRs, resulting in its internalization [14] and inhibiting B-cell antigen presentation of both BCR-dependent and BCR-independent antigens [15], observations that suggested a broad potential for anti-Id recognizing that may involve extra- and intra-cellular interactions.

An additional significant aspect of anti-Id antibodies and BCRs or TCRs interactions was explored later in 2013 by Jacobsen et al. [16]. Using transfected B lymphoma cells, these researchers could demonstrate that anti-Id BCRs can directly conjugate to their paired Id BCRs, inducing signaling and eventually apoptosis [16]. In 2014, Jacobsen et al. [17] also established that naive anti-Id B cells can collaborate *in vivo* with T cells, even at low frequency. This interaction could result in germinal center formation, plasma cell development, and the detection of soluble isotype-switched anti-Id antibodies [17]. This study could also demonstrate that this effect is not dependent on anti-Id antibody processing and presentation by dendritic cells, suggesting that it is mediated by intact anti-Id antibodies, which opens the prospect for therapeutic approaches. In the same year, IVIg was also demonstrated to naturally recognize some BCRs, promoting a specific long-term functional silencing program similar to anergy [18].

Although historically abundant, scientific evidence exploring these idiotypic interactions mediated by IgG still holds significant technical limitations. The pattern of anti-Id antibody production is influenced by naturally developed and environmentally-stimulated IgG repertoire, resulting in individually distinct anti-Id IgG repertoires for individual immunological backgrounds. Consequently, these different anti-Id IgG repertoires may differentially interact with TCRs and BCRs, inducing differential effects. This aspect was considered in a hypothesis called "the hooks without bait" [19]. This hypothesis discussed the diversity of possible modulatory implications mediated by natural and induced anti-Id IgG antibodies on several populations of B and T cells with modulatory and regulatory functions and may generate some experimental pathways for future investigations.

However, knowledge of the anti-Id antibodies' interactions with TCRs, BCRs, and their role as mediators of immunoregulation has always been secondary in the literature and underexplored in non-autoimmune inflammatory diseases, including atopic dermatitis (AD).

Although AD is one of the most common dermatological diseases, its pathogenesis remains understood. It was recently demonstrated that AD had a complexity of its endotypes, re-

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vealing at least four AD types [20,21]. These endotypes can be distinguished by biomarkers clusters and are termed as "skin-homing chemokines/interleukin (IL)-1 receptor type 1-dominant" cluster, "Th1/Th2/Th17-dominant" cluster, "Th2/Th22/pulmonary and activation-regulated chemokine-dominant" cluster, and "Th2/eosinophil-inferior" cluster [22]. These observations indicate that the complexity of AD pathogenesis implicates complex and diverse interactions between naturally developed or induced cells and molecules to be better determined. The biological reasons that yield the identification of such distinct AD endotypes need elucidation but possibly involve several conserved and clonal receptors expressed on T- and B-cell membranes, rendering functional alterations with implications in the development and severity of AD.

Therefore, aiming to bring a historical discussion about the immunoregulatory effects mediated by anti-Id antibodies, mainly of the IgG isotype (the most abundant in human circulation), to some recent approaches based on a frequent but not an elucidated dermatological disease as background, we proposed here a brief review of *in vitro* and *in vivo* evidence that may demonstrate the importance of this topic as a generator of innovative therapeutic protocols to control the development of AD with possible applications to other atopic and non-atopic immunological disturbances.

Experimental Evidence on the Immune Tolerance Induced by IgG

In 2010, it was demonstrated in a murine m odel of allergy induction that the passive transference of anti-allergen IgG to pregnant mice could induce the IL-10 production by offspring T cells (T regulatory cells termed as Tr1) in the absence of antigen, suggesting a murine *in vivo* anti-Id mediated mechanism [23]. More recently, it was demonstrated in a similar murine model of allergy induction that the injection of homologous (mouse) or heterologous (human) anti-Id IgG could attenuate allergic responses in both *naïve* and allergen-immunized mice [24]. This study could conclude that the IgG treatment protocols produced a long-lasting suppression of allergy (14 weeks) and that the effects seem to depend upon the induction and expansion of T regulatory cells.

Using IVIg *in vitro*, it was demonstrated that a natural human IgG repertoire could decrease T cell proliferation in adult peripheral and umbilical cord blood [25]. Furthermore, this study showed that IVIg could inhibit anti-CD3-induced but not phorbol ester-induced T cell activation and IL-10, IL-2, and interferon-gamma (IFN-γ) production, suggesting a direct T cell immune modulation by dampening TCRs responses, which possibly include anti-Id antibodies-mediated recognition.

In 2018, using an *in vitro* standardized protocol of human thymic lymphocyte culture with purified IgG, it was demonstrated that pooled IgG from AD patients could modulate thymic CD4+ T cells cytokine production. This study indicates that IgG from AD patients induced the production of IL-17 and IL-10 by intrathymic immature double positive (DP) and mature CD4+ T cells compared to IgG from healthy individuals [26]. In a similar *in vitro* protocol, it was demonstrated in 2020 that pooled IgG from AD patients could induce thymic invariant natural killer T, CD1d-restricted T cells that employ an invariant TCR alpha chain and a limited repertoire of beta chains to produce higher levels of intracellular IL-4, IL-10, and IL-17 when compared to IgG from healthy non-atopic individuals [27].

More recently, it was demonstrated that purified IgG from AD individuals could induce overexpression of cutaneous lymphocyte-associated antigen (CLA) on thymic CD4+ T cells since its immature DP stage *in vitro*, an effect that was not observed on CD8+ T cells, where an opposite effect was revealed [28]. This observation was relevant because CLA-expressing CD4+ T cells can be considered a peripheral biomarker of AD [29]. Therefore, this observation also suggested that purified IgG from AD patients may modulate intrathymic T cell maturation, favoring the migration of CD4+ T cells to the skin. The same study also reveals that purified IgG from AD patients can induce thymic CD4+ T cells to acquire an intense IL-22-production profile (Th22) and modulate the expression of several micro RNA with modulatory functions. Additionally, this study revealed that the observed effect is not a consequence of IgG isotype variations and that IgG from AD patients can directly interact with DP T and CD4+ T cell membranes.

Some *in vitro* studies have also demonstrated that atopic IgG repertoire can modulate CD8+ T cell functions. Recently, it was shown that IgG from atopic individuals could induce non-atopic infant thymic and adult peripheral CD8+ T cells to produce IL-4, acquiring a TC2 profile [30]. However, this study did not investigate if this effect was mediated by the direct interaction of IgG with CD8+ T cell membrane, not even TCRs.

In addition to idiotypic interactions that may occur with membrane proteins, a study performed in 2015 suggested that IgG also permeates cells and interacts with intracellular molecules, inhibiting T-cell activation after its interaction with nuclear and cytoplasmic components [31]. These cell-penetrating

antibodies, which could be detected in IVIg formulations, penetrate various mammalian cell lines and represent approximately 2% of IVIg. This possibility also needs to be discussed because it suggests that anti-Id IgG may interact with TCRs intracellularly, still at an early stage of production of these receptors.

A very recent approach evaluating IgG from AD patients could also yield some observations about unconventional gamma-delta (γδ)T cells. This study assessed the effect of IgG from AD patients on non-atopic neonatal thymic γδT cells and demonstrated that IgG from AD patients could downregulate the expression of α4β7 and up-regulate the expression of CLA homing molecules on γδT cells. This study suggested that IgG from AD patients may exert some role in modulating homing properties of T cells during its maturation on the thymus, inducing a skin-homing profile (CLA+), which may corroborate with the elucidation of AD development [32]. Additionally, the same study demonstrated that IgG from AD patients induced the production of IFN-γ, IL-17, and IL-22 and reduced the apoptosis on thymic γδT cells, corroborating not only with a skin-homing profile but also a cytokine secretion profile and an anti-apoptotic profile that may play some role on AD development.

Together, these results cannot fully elucidate the primary mechanism by which purified IgG from AD patients can mediate immunoregulatory effects, not even demonstrating idiotypic interactions between IgG and TCRs as a pivotal interaction mediating the observed immunomodulatory effects.

Other studies observing the human and murine effect of purified IgG according to its repertoire had been performed to evaluate not only AD patients-derived IgG but also different repertoires of IgG from which we may also acquire some interesting knowledge.

Some *in vitro* experiments comparing the effects of IgG obtained from atopic (allergic non-AD) or non-atopic individuals could demonstrate that even at low doses, IgG obtained from non-atopic individuals induces the production of IFN-γ by CD4+ and CD8+ T cells what was not observed in the presence of IgG from atopic individuals or the commercially used IVIg [33]. Those observations suggested that IgG from non-atopic individuals may favor the maturation of a non-atopic profile by CD4+ and CD8+ T cells, corroborating with the development of an allergen-tolerant profile.

In a translational approach developed from a murine model of allergy, some *in vitro* experiments performed using IgG from atopic patients could demonstrate the induction of IL-17 production by thymic and peripheral γδT cells and an opposite effect using IgG from healthy non-atopic individuals [34]. Also, in the context of unconventional T cells, it was demonstrated that IgG obtained from non-atopic individuals could induce the production of IFN-γ and IL-10 by thymic but not peripheral γδT cells compared to IgG from atopic patients [35]. The same study demonstrated that IgG from atopic patients could induce the production of IL-17 by peripheral γδT cells compared to IgG from non-atopic individuals. These observations are relevant because they suggest that differential effects could be observed when IgG repertoires interact with immature or mature T cells, an experimental aspect that must be considered when transposing results from *in vitro* to *in vivo* conditions.

Lastly, an additional study could demonstrate that a differential effect of IgG repertoires may be influenced not only by atopic diseases but also by virus exposure or infection. The authors demonstrated that IgG from human immunodeficiency virus (HIV)-1-exposed seronegative (ESN) and HIV-1-infected subjects could differently modulate the production of IFN-γ thymic T and B cells, while IgG from ESN could induce the production of IFN-γ by γδT and B cells, IgG from HIV-1 could induce the production of IFN-γ by CD4+ and CD8+ T cells [36]. These observations open a broad spectrum for investigations on elucidating resistance mechanisms and susceptibility to infectious diseases.

These AD and non-AD evidence corroborate the hypothesis that IgG can effectively mediate modulatory functions in a repertoire-related pathway and reinforce the need for more elucidative studies in this field.

Some general aspects of this discussion must be highlighted. First, most of the experimental approaches cited above used an IgG concentration that can be considered low compared to physiological conditions and expected levels detected in patients under IVIg therapy. This aspect may collaborate with the practice and safety of *in vivo* protocols. Second, almost all approaches were performed with heterologous IgG between mice and species (mice and humans), indicating a potential for commercial development of therapies. In this last aspect, it is interesting to observe an experimental approach performed using combinations of both heterologous and homologous immune IgGs from mice and humans. Both could produce a long-lasting suppression of allergic immunity, even in pre-sensitized animals [24]. These observations corroborate the suggestion that both sources of IgG can exert regulatory functions.

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In Vivo Approaches to the Immune Tolerance Induced by IgG Administration

In the early 1990s, it was demonstrated that the treatment of four AD children with high doses of IVIg (400 mg/kg) for 5 days as therapy for the coexisting Kawasaki syndrome or idiopathic thrombocytopenic purpura could be related to improved skin scores, decreased immunoglobulin E (IgE) levels, and reduced eosinophil counts for more than 6 months [37]. From this observation, some scarce evidence about treating AD patients with IVIg can be found in the literature, but some need to be highlighted.

In 2000, Jolles et al. [38] reported their experience using high doses of IVIg (2 g/kg) as adjunctive therapy with prednisolone and hydroxychloroquine to treat three patients with resistant AD. This study evaluated the eczema skin scores monthly, and all patients demonstrated improved scores. Later, in 2005, Bemanian et al. [39] compared the use of high doses of IVIg (2 g/kg) with oral cyclosporine in the treatment of severe AD, and they observed that IVIg treatment could improve clinical signs and symptoms, but the therapy with cyclosporine resulted in a better improvement. Considering that IVIg is an expensive and periodic treatment compared to cyclosporine, which is relatively cheap, more available, safer, and more effective in improving clinical signs, the author did not indicate IVIg as a treatment for severe AD.

Some years later, in an innovative approach directly related to our discussion, Nahm et al. [40] published the results obtained with a pioneer autologous immunoglobulin therapy protocol tested in three adult patients with severe AD. These patients received low doses of autologous IgG (50 mg) twice a week for 4 weeks and were followed for more than 2 years, a relatively low dose compared to IVIg protocols. The results revealed that two patients showed long-term clinical improvement for more than 36 weeks after therapy with decreased clinical severity scores, serum total IgE concentrations, and decreased peripheral eosinophil counts without significant side effects [40]. One year later, the same group demonstrated in a larger group of AD patients (n=16) that the same autologous immunoglobulin therapy protocol could significantly decrease the serum levels of anti-dust mite IgE and simultaneously increase the serum levels of anti-dust mite IgG4, IL-10, and IFN-γ [41]. This previous study suggested that the immunoregulation induced by the autologous AD IgG administration can positively affect the development of an antigen-specific allergic reaction, offering a broader regulatory potential for IgG, as suggested by the experimental evidence discussed above.

Three years later, a randomized clinical trial was performed with a similar autologous immunoglobulin therapy protocol cited above. This time, autologous IgG was administered at the same 50 mg dose but with 8 weekly intramuscular administrations. In this trial, the researchers compared AD patients who received autologous IgG with AD patients who received a placebo and observed decreased clinical severity score and reduced incidence of AD exacerbation, reduced affected area, improved Dermatology Life Quality Index, and again, increased serum levels of IL-10 and IFN-γ [42]. These results consolidate, at least in part, the experimental suggestions about the potential of an IgG repertoire obtained from AD patients in regulating the development of clinical atopic manifestations.

The results of the first clinical trial in healthy human subjects that evaluated the immunomodulatory effect of autologous IgG therapy were recently published. In this study, 13 healthy adults were submitted to an intramuscular administration of total autologous IgG in the same protocol used in the above AD patients' studies (50 mg for 4 weeks). These individuals demonstrate an increase in the percentage of peripheral CD4+ T cells producing IL-10 and CD3+ T cells producing IFN-γL-10 compared to baseline [43]. Unfortunately, the researchers did not evaluate complex intracellular and phenotypic molecules to generate more analytical aspects that may be compared or corroborated with the complexity of experimental evidence. However, this study broadened interest in the therapeutic potential of using IgG in humans.

All the *in vivo* approaches cited above were performed using autologous IgG. However, several pieces of evidence from the knowledge obtained with IVIg therapies, some mentioned in this review, indicate that similar effects may be obtained with intravenous administration of heterologous polyvalent human IgG. Though audacious, it might be possible to suggest that heterologous AD IgG may represent a therapeutical possibility to be evaluated in the following years.

Future Directions

After summarizing the results directly related to *in vitro* and *in vivo* experiments with IgG from AD patients (Fig. 1), we may consider future protocol diversification directions. It will be essential to perform more *in vitro* experiments that may evaluate the effects of IgG from AD patients on peripheral cells and encompass more diverse cell populations. Some approaches

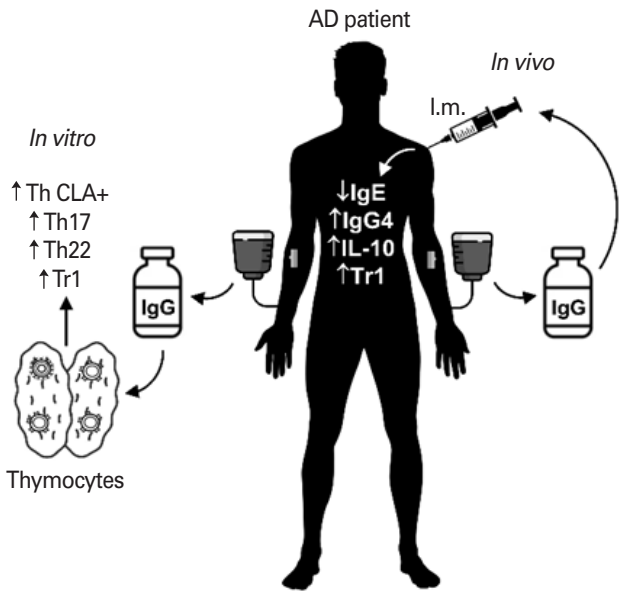

Fig. 1. Graphical abstract summarizing the effects mediated by immunoglobulin G (IgG) from atopic dermatitis (AD) patients from studies performed *in vitro* and *in vivo*. Left indications refer to *in vitro* approaches that were performed using protocols where the purified IgG obtained from AD donors were cultured with healthy thymocytes for less than 7 days, and the phenotype or cytokine production on the T CD4+ cells (Th) profile was evaluated. Right indications refer to *in vivo* approaches where the purified IgG obtained from AD donors were autologous injected by the intramuscular (I.m.) route, and the levels of circulating antibodies/cytokines or the frequency of interleukin-10 (IL-10)-producing T CD4+ cells (T regulatory cells, Tr1) frequency were evaluated. CLA, cutaneous lymphocyte-associated antigen; IgE, immunoglobulin E.

assessing possible effects on dendritic cells, unconventional T cells, and B cells must be considered. In *in vivo* experiments, the promising results obtained with autologous IgG from AD patients must be compared with a heterologous source of IgG. The standardization of protocols using heterologous IgG may facilitate opportunities for commercial exploitation, which would facilitate access to this type of therapy.

From a historical and broader perspective, since the 1980s, it has been demonstrated that AD patients can produce detectable levels of IgG anti-IgE antibodies [44] and that these antibodies can mediate inflammatory mediators released from basophils and mast cells [45]. This observation was recently confirmed by two similar studies where the functional activity of IgG anti-IgE autoantibodies from patients with AD was evidenced by the release of pro-inflammatory mediators and cytokines from human basophils and mast cells [46,47]. From our point of view, considering that IgG anti-IgE antibodies are present and functional in AD patients' serum, it is possible that the induction of immunity by IgG administration can yield the production of specific anti-Id IgG that collaborates with a repertoire that can neutralize IgG anti-IgE antibodies, mitigating IgG-mediated pro-inflammatory functions, and collaborating with the acquisition of a regulatory profile by T- and B-cells. Together these components may mediate disease control, but this issue needs elucidation.

Another unsolved question to be investigated is related to a recent study where the IgG-reactivity towards 1,152 human protein fragments was evaluated in 80 individuals (AD patients and healthy controls). In this study, the authors could detect a significant differential IgG-reactivity to four antigens representing keratin-associated protein 17-1, heat shock protein family A member 4, and S100 calcium-binding proteins A12 and Z. The reactivity to these antigens was more frequent in the severe AD patients (66%) compared to moderate AD patients (41%) and healthy controls (25%) [48], suggesting that the natural IgG repertoire of AD patients may also include the recognition of conserved molecules and differs according to AD severity.

Similarly, a study investigating the origin of natural IgE production by AD patients evaluated antibody variable-heavy region hypermutation levels in AD patients. The results indicate that the natural IgG repertoire in AD patients differs from non-allergic healthy subjects [49], corroborating the hypothesis that AD development and control may be related to developing a specific IgG idiotypes repertoire. These aspects of AD patients' repertoire and the recognition of conserved molecules also need elucidation.

Another recent study could demonstrate differences in the diversity of the IgG repertoire from AD patients, comparing AD subgroups (severe or moderate) or healthy controls. The authors could support an association between AD and IgE autoantibodies and between AD and a higher prevalence of anti-nuclear antibodies, but the data was insufficient to relate AD and other indicators of autoimmunity [50]. Again, this evidence corroborates the demonstration of a differential specific IgG idiotypes repertoire from AD patients compared to healthy individuals or other groups of donors. Together, these studies reinforce the importance of future detailed assessments of the IgG repertoire produced by AD patients and corroborate the hypotheses that AD patients develop a unique IgG repertoire that may be susceptible to anti-Id-mediated immunoregulation.

In recent years, evaluating a complete set of IgG idiotypes

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obtained from human donors has become technically possible. Some technologies termed epitome and proteome microarrays propose simultaneously assessing IgG idiotypes' reactivity to thousands of human or microorganism-derived molecules. In this topic, it is essential to consider the IgG reactivity to microorganisms because of the influence that commensal bacteria can exert, stimulating the production of antibodies, including IgG [51]. This antibody production may strengthen the communication between mucosal and systemic immune compartments exerting modulatory or regulatory functions on developing several diseases. Furthermore, it was already demonstrated in young children that the severity of AD might be associated with an IgG response directed against *S. aureus* antigens, corroborating the theoretical possibility that the IgG repertoire can be effectively related to AD development [52].

When performed, those investigations will collaborate on elucidating the "hooks without bait" theory [19], where the sets of idiotypes, regardless of the biological reason necessary to stimulate it, may reveal some relationship with the immunomodulatory effects. These results may generate therapeutical applications not only for AD and atopic diseases but also for autoimmunity and other diseases related to immune dysfunctions.

Conclusion

In the current state of the art, it is not possible to predict if the analyses of the IgG sets of idiotypes will generate the identification of conserved or clonal molecules that can be chosen as targets. However, it is interesting to indicate that due to the efficient development of monoclonal antibodies for therapeutic use in recent years, clonal or conserved targets that were identified may be reached using monoclonal anti-target antibodies, anti-Id antibodies or synthetic molecules designed for inducing the expected effects.

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