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Genetic Crosslinks Between Autoimmune Diseases and Selective Immunoglobulin A Deficiency and Its Role in Assessing Cholera Vaccination Outcome

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Abstract

Polymorphic genes of human leukocyte antigen (HLA) class II were linked to an individual's immune response and the development of autoimmune diseases. This is a common genetic background between selective immunoglobulin A deficiency (sIgAD) and autoimmune deficiency, including type-1 diabetes (T1D). sIgAD is considered the most common type of primary immunodeficiency (PID), and sIgAD individuals are defective in the production of sIgA, which is crucial in providing mucosal immunity against several enteric pathogens that enter the human body through the nasal or oral cavity affecting an individual's overall gut. sIgA is found in body secretions, including breastmilk, mucus, and saliva. Significant levels of circulating sIgA in an individual's mucus are crucial to a successful cholera vaccine; however, in breastfeeding mothers, the level of sIgA in the breastmilk provides herd immunity to their infants. Breastfeeding mothers that suffer from sIgAD cannot provide herd protection, which affects the cholera vaccine efficacy resulting in insignificant immunity observed in infants after direct vaccinations, thus making them dependent on their mothers for immunity. However, there is no routine check for the diagnosis of sIgAD, and the individuals are often asymptomatic. Therefore, the association of the disease with autoimmune diseases can serve as a tool in diagnosing the disease during cholera vaccination campaigns and sensitization.

Keywords: sIgA; cholera; autoimmune diseases; T1D, sIgAD; *Vibrio cholerae*

Introduction

Immunoglobulin A (IgA) is a component of an advanced B-cell-mediated immune response, a humoral response of the adaptive immune system. It is known to be the most abundant immunoglobulin in the body, and it was reported that the human body synthesizes about 3-5g per day of IgA, which is circulated in the blood and as an immunogenic component of body secretions such as mucus, breast milk, and saliva (Yel, 2010). Another report indicated that the body produces that amount of IgA daily in response to the detection of invading pathogens, and the amount is more than the total amount of other immunoglobulins isotypes produced (Pabst, 2012). The mucosal surface of the gut and nasal regions serves as the first line of defence against mucus-invading pathogens such as *Vibrio cholerae*, and the secretive (selective) IgA (sIgA) is the most crucial and predominant immunoglobulin in the mucosal surfaces, protecting the body against tons of invading pathogens it is exposed to daily (Vo Ngoc et al., 2017). sIgA is considered the most vital antibody to protect humans from *V. cholerae* infection, and because it is found in breast milk, it is critical in protecting infants. Infants and younger children are the most affected age group during cholera epidemics, and cholera vaccinations proved to be inefficient in providing protective immunity against *V. cholerae* in the age group (WHO, 2017), thus breastfeeding serves as a source of sIgA to infants from their mothers.

Selective IgA deficiency (sIgAD) is a genetic defect in the production of sIgA in the body, resulting in weakened mucosal immunity. Therefore, individuals with sIgAD cannot produce sufficient sIgA after cholera vaccination, thus showing weak vaccine outcomes. However, sIgAD is not routinely

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checked, and since the individuals are mostly asymptomatic, it is rather challenging to consider that. Several autoimmune diseases, including type-1 diabetes (T1D), have been associated with sIgAD, suggesting that the two conditions may have a common genetic background (Amaya-Uribe et al., 2019; Wang et al., 2011). Recently, it was demonstrated that the polymorphic genes of human leukocyte antigen (HLA) class II are critically involved in regulating both components of the human immune system (innate and adaptive) and autoimmunity, supporting the previous claims that both sIgAD and autoimmune diseases such as T1D may share a common genetic basis (Cun et al., 2021). Several polymorphs of the HLA class II genes have been identified to be involved, including DRB1, DPB1, DRA, DQA1, DQA2, DQB2, and DPA1, and are illustrated to be located on the short arm of chromosome 6, specifically in the major histocompatibility complex (MHC) class II locus (Trowsdale 2011). However, in T1D individuals, specific HLA haplotypes of the genomic region of MHC class II including DR3/4, DQ2/8, and HLA-B8 are found to be present in about 90% of the cases (Tait et al. 2007 and Leslie et al., 2008)). Interestingly, in sIgAD individuals, DR3, DQ2, and HLA-B8 haplotypes have been predominantly associated with the sIgAD (McDonald-McGinn et al., 2015), and these separate findings indicate the genetic link between T1D and sIgAD. Therefore, this common HLA predisposition in both cases may explain the overlap between sIgAD and T1D, since the 8.1 haplotype variant involved in the two cases might serve as a risk factor for developing sIgAD and autoimmune diseases such as T1D (Amaya-Uribe et al., 2021).

sIgA

The mucosal humoral immunity depends largely on sIgA; thus, it is suggested to be an important marker of the immune integrity of the mucus. sIgA is produced in the mucosa and exits in a dimeric form capable of neutralizing intraluminal pathogens; it is also reported to be the predominant immunoglobulin on intestinal surfaces (Arkwright et al., 2002). The sIgA antibodies are structurally designed to resist the hostile environment of the mucus, withstanding chemical and enzymatic degradation from both the human body and the gut microbes (Mantis et al., 2011).

However, individuals with sIgAD are demonstrated to have a defective immunoglobulin class switching or a defect in the terminal differentiation of the IgA plasmablasts into secretory forms (sIgA) found in secretions and the duration of survival of the plasma cells responsible for the secretion of the IgA (Cipe et al., 2013). In some cases, there is also a significant decrease in IgA-bearing B lymphocyte count (Yel, 2010).

Furthermore, in peripheral B cells, the impairment in the rearrangement of the switch (S) μ to Sα has been reported in sIgAD patients (Yazdani et al., 2017). However, the major defect observed in individuals with sIgAD is a defective switching of IgA-bearing B lymphocytes to IgA-secreting plasma cells (Cinicola et al. 2022), implying that the IgA may be produced. Still, it cannot be found in important secretions such as mucus or breastmilk, where the sIgA plays a significant role in protecting against invading microbes in adults and breastfeeding infants. Individuals with sIgAD have decreased levels or a complete lack of IgA antibodies in their body; it is characterized by less than 0.07g/L of IgA in the serum while having a normal concentration of immunoglobulin M (IgM) and immunoglobulin G (IgG) in individuals of age 4 and above (Yazdani et al., 2017).

sIgA protects the gut epithelium against pathogenic microbes by acting as a host-specific colonization resistance mechanism. The resistance mechanism prevents pathogenic microbes from adhering, colonizing, and penetrating the mucus, aiding in their clearance from the gut and thus avoiding infection. Therefore, sIgAD individuals are more likely to be susceptible to enteric infections and have a poor enteric vaccine response (Sutherland et al., 2016), possibly due to a loss of an important component of the mucus immune system. Interestingly, it was illustrated that the sIgA is crucially involved in regulating gut microbiota composition and function, hence the overall health of an individual (Catanzaro et al., 2019). Moreover, gut dysbiosis has been observed in most sIgAD individuals compared to healthy individuals; this is due to weakened mucosal integrity that leads to an increased and decreased abundance of pathogenic and commensal microbes in the gut, respectively (Catanzaro et al., 2019; Kubinak and Round, 2016). The Catanzaro team further illustrated that the role of sIgA in the body cannot be replaced effectively by the less specific IgM counterpart, concluding that sIgAD individuals will have a dysbiotic gut despite an average level of IgM. It is worthy of note that normal gut microbiota plays a crucial role in protecting against invading pathogens such as *V. cholerae* by deploying different microbe-specific colonization resistance mechanisms such as antimicrobials, quorum sensing, nutrient competition, and immune system activation (Ducarmon et al., 2019).

Genetic background of sIgAD and its prevalence

sIgAD is commonly associated with a defect in the MHC class II locus, precisely on the HLA class II polymorphic genes, as mentioned earlier. It is reported that about 45% of individuals with sIgAD have at least a single copy of the HLA-B8, -DR3, and -DQ2 haplotype, which is more than three folds compared to the general population (Matsuda et al., 2020; Mohammadi et al., 2010). The reports from Mohammadi et al. added that the risks of developing sIgAD are increased when there is homozygosity of the ancestral haplotype. However, it is worthy of note that the genetic basis of sIgAD is not entirely from the MHC class II genes as described in some studies. It was reported that a polymorphism in regions of some non-MHC class II genes such as interferon-induced helicase 1 (IFIH1) have been reported to be associated with sIgAD, as observed more than a decade ago in a genome-wide association study (GWAS) (Ferreira et al., 2010).

Moreover, about 10 to 15% of individuals with sIgAD were reported to have mutations in some genes associated with B and T cells, including genes coding for B cell activator factor – receptor (BAFF-R), CD19, and tumour necrosis factor superfamily 13 (TNFRSF13B) (Rachid et al., 2006). Furthermore, distinct from genetic factors, some epigenetic changes, including infections, have been described to be associated with sIgAD development. Some of the epigenetic factors identified exert their effect mostly by altering the methylation states of the TNFRS13B and C genes that correlate with mRNA expressions of BAFF-R and transmembrane activator and calcium-modulating cyclophilin ligand interaction (TACI) and hence the availability of IgA levels (Zhang et al., 2021). A decreased expression of complete IgA mRNA in the secreted and membrane forms of IgA in both the normal and defective IgA-switched B cells is demonstrated to be found in sIgAD individuals (Wang et al., 1999). However, generally, certain HLA haplotypes from both MHC class I and II (8.1 haplotypes), specifically HLA-A1, -B8, -DR3, -DQ2 are the frequent haplotype that is found in sIgAD patients, and they are potential risk factors in the development of sIgAD (Ferreira et al., 2010; Urbonas et al., 2016), but do not restrict the development of sIgAD to MHC genes as described above. The genetic background of sIgAD is summarized in Table 1. These findings indicate that sIgAD is highly associated with autoimmune diseases, and since sIgAD has no specific routine screening, this connection can be used to diagnose sIgAD.

Table 1. sIgAD genetic backgrounds.

Genetic background	Genes involved	Reference
MHC genes	HLA-DR3, -DQ2, -B8.	Matsuda et al., 2020
Non-MHC genes	IFIH1, BAFF-R, CD19, TNFRSF13B and C, B & T cell genes.	Rachid et al., 2006 ; Ferreira et al., 2010
Epigenetics	TNFRS13B and C.	Zhang et al., 2021

The sIgAD prevalence depends on many factors, such as the family history of the disease and the country of origin. Concerning the family history, the heterogeneity in inheritance is reported to be a result of a genetic defect, including deletions in the genomic sequence of heavy chains of IgA1, IgA2, and IgG on chromosome 14, which can be inherited in different ways (Zhang et al., 2021). Consequently, first-degree relatives are reported to be more prevalent to develop sIgAD, at a 38 times higher rate than unrelated individuals, and about 20% of sIgAD cases are inherited as was reported based on pedigree analysis (Owen et al., 1982). Moreover, the risk of getting sIgAD was shown to increase when an individual's mother has sIgAD than when the father has it, by 20.1% compared to 5.8% respectively. This is due to paternal imprinting of IgAD susceptible genes and also suggests that epigenetics is involved in the development of sIgAD (Zhang et al 2021). Furthermore, sIgAD is demonstrated to be common in individuals with a family history of common variable immunodeficiency (CVID), which according to the report by WHO in 1995, is characterized by a decreased serum level of IgA, IgG, and in 50% of such cases, reduced IgM levels are reported. It was also concluded that there is an occurrence of both CVID and sIgAD in families due to a shared genetic defect concerning a shared susceptibility in loci and alleles (Orange et al., 2011).

Interestingly, consanguineous marriages are shown to increase the number of cases, therefore, countries with high rates of such marriages will have multiple instances than where there are not (Oen et al., 1982). Conclusively, it was illustrated

that sIgAD prevalence is about 1:700 worldwide. However, this prevalence ranges from 1:132 to about 1:18500 based on the population that was analyzed (Lilic et al., 2001). Because most sIgAD patients are asymptomatic, there is a lack of an established routine screening for the deficiency and hence the results obtained on the prevalence of the deficiency could be higher (Haris, 2018).

V. cholerae and sIgA

V. cholerae is a facultative anaerobe, comma-shaped enteric pathogen, rapidly transmitted through the faecal-oral route and is known to be the causative agent of cholera infection, characterized by painless vomiting and profuse diarrhoea (Millet et al., 2014). However, to be able to cause infection, the pathogen must survive colonization resistance mechanisms in the gut, penetrate the thick mucosal layer, and then attach itself to the intestinal epithelium to release cholera toxin (CT) (Sharmila and Thomas, 2018). Intriguingly, sIgA is considered to be the predominant Ig of the mucus and is crucial in protecting against *V. cholerae* (Haris, 2018). The CT is responsible for the cholera symptoms, and sIgA antibodies against CT are produced in the body and function to identify and block its activity. Mechanistically, sIgA has been demonstrated to trap and inhibit *V. cholerae* in the gut environment and/or the mucosal layer, thereby blocking its colonization and attachment to the intestinal epithelium and thus preventing cholera infection (Levinson et al., 2016; Wang et al., 2016). Hence, after cholera vaccination, a higher level of circulating sIgA antibodies predicts a strong correlation between vaccine efficacy and protection against *V. cholerae* infection. For immunity against cholera infection, long-lived sIgA-producing plasma cells can provide protective immunity. However, the immunity is reported to collapse after 6 months in younger children and up to 5 years in older children and adults (Uddin et al. 2011). In older individuals, however, cholera toxin subunit B (CTB)-specific sIgA was reported to be detected in body secretions such as saliva, breast milk, and even intestinal fluids after vaccinations (Leung et al. 2012). In another report, it was demonstrated that an increased level of CT-specific sIgA was observed in adults three days after receiving the second dose of vaccination, which is fifteen months after the first vaccination proving an anamnestic response (Svennerholm et al., 1984). Surprisingly, it was demonstrated that CT-specific IgM and IgG memory B cells are not involved in protecting against *V. cholerae* infection (Haney et al., 2018). Therefore, for an efficient cholera vaccine, research has focused on effectively inducing *V. cholerae* pathogen-specific sIgA and other immune responses (Boyaka, 2017). Thus, individuals with sIgAD are susceptible to *V. cholerae* infection, and their response to cholera vaccinations will be poor compared to the general population due to the defect in achieving a significant level of pathogen-specific sIgA antibodies.

sIgAD and autoimmune diseases

The association between sIgAD and autoimmune diseases such as T1D has long been established; both conditions have a common genetic background involving the HLA haplotypes such as HLA-A1, -B8, -DR3, and -DQ2 genes. The prevalence of sIgAD in individuals with autoimmune diseases was estimated to range between 5 to 30% (Aghamohammadi et al., 2011; Shkalim et al., 2010; Yazdani et al., 2015). Conversely, it was demonstrated that individuals with sIgAD commonly suffer from autoimmune diseases such as T1D, coeliac disease, thyroiditis, and rheumatoid arthritis (Wang et al., 2011).

Distinctive from the common genetic and epigenetic basis of sIgAD and T1D, it was suggested that due to the lack of sIgA in the mucosal secretions in individuals with sIgAD that eventually resulted in dysbiosis and hence several immunological changes may also contribute to the development of autoimmune diseases including T1D (Soheili et al., 2013). This stipulation can further be supported by another finding which reported an increased level of autoimmune antibodies observed in sIgAD patients. This increase is suggested to be from mechanisms such as molecular mimicry and possible cross-reaction with self-antigen (Jacob et al., 2008).

Furthermore, individuals with sIgAD have been associated with abnormal T cell regulation (Treg), including CD4+, which is commonly known to eventually result in the progression of immune tolerance and hence the development of autoimmune diseases (Arkwright et al., 2011). Figure 1 summarizes the relationship between sIgAD and autoimmune diseases such as T1D. Further studies are required to strengthen the already established correlation between sIgAD and autoimmune diseases and possibly more connections between them. These findings can be useful in the screening of sIgAD amongst the population.

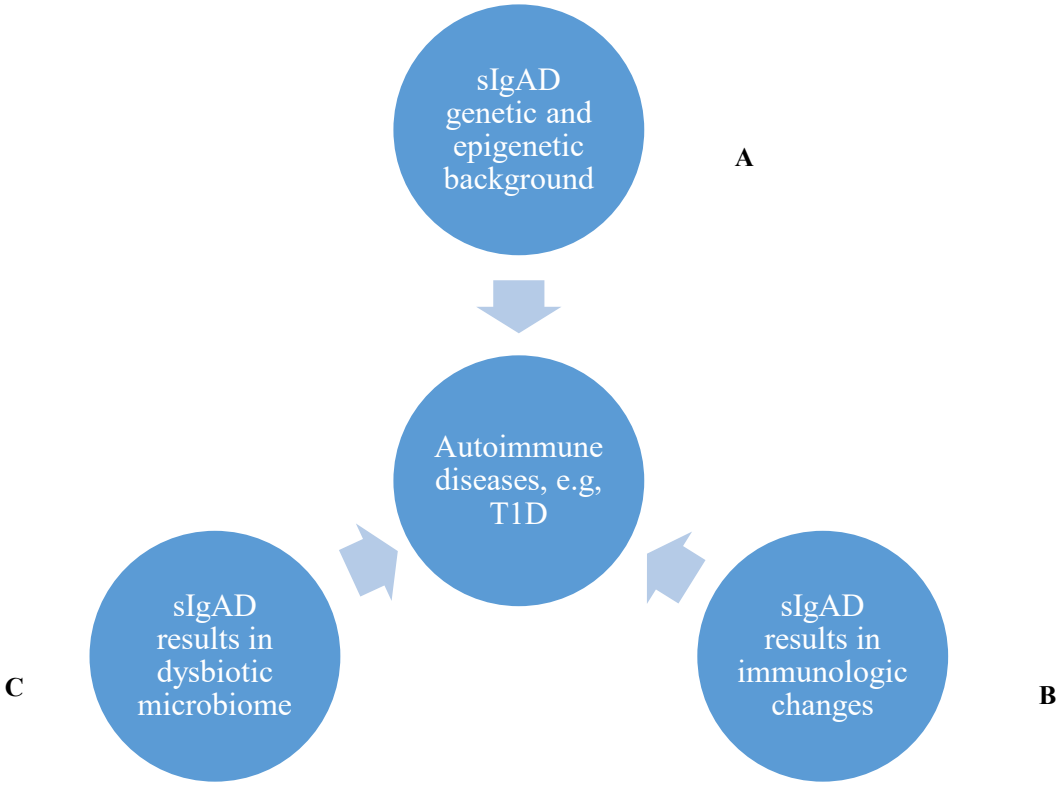

Figure 1. (A) sIgAD has been extensively demonstrated to share the same genetic background involving the HLA haplotypes. (B) sIgAD leads to abnormal T cell regulatory cells (Treg) such as CD4+, resulting in the development of autoimmune diseases. (C) The decrease in sIgA in sIgAD individuals was described to lead to dysbiosis that may also cause immune impairment, resulting in the development of autoimmune diseases.

Conclusion and future perspectives

sIgA is considered to be a hallmark of mucosal immunity, and its relevance is crucial in the body's defence against several mucosal enteric pathogens such as *V. cholerae*. sIgAD individuals are hence susceptible to gut enteric infections such as cholera due to weakened specific mucosal immunity, and that will affect the vaccine efficacy in these individuals. Since individuals with sIgAD are mostly asymptomatic, thus, there is no specific attention given to the deficiency, such as devising a routine screening for the disease condition. Therefore, most cases are often undiagnosed. Vaccinations against enteric pathogens such as *V. cholerae* aim to boost the production of IgA and sIgA against the pathogen, and their level in circulation corresponds to the vaccine efficacy. Consequently, cholera vaccines are focused on providing sufficient IgA and sIgA, specifically the sIgA found in secretions such as breastmilk, which thus can be passed from a breastfeeding mother to her infant. This type of immunity is known as herd immunity and is crucial in current cholera vaccinations. The three oral cholera vaccines (OCVs) prequalified by WHO target infants through herd immunity due to insufficient immunity observed after direct vaccination of infants and younger children at the age of 5 and below. Moreover, since sIgA is found in secretions such as breastmilk and mucus, a defect in sIgA will affect the overall immunity in adults, which will be worsened if the nursing mother are having its deficiency. The herd protection is also lost. Therefore, targeting sIgA in cholera vaccination is critically important since other antibodies, such as IgM and IgG, are considered ineffective in protecting against cholera infection. The sIgAD can be an explanation for poor sIgA obtained after vaccinations in some individuals. Considering the prevalence of sIgAD in a population and for the autoimmune disease, which can be about 5 to 30% of individuals with autoimmune diseases, this is enough to affect cholera vaccine efficacy within a population. Diagnosing sIgAD individuals concerning cholera vaccination is crucial, especially in nursing mothers whom their infants rely fully on for their sIgA protection against cholera infection. Unfortunately, there is no routine test to specifically diagnose sIgAD; however, during vaccination campaigns and sensitization, individuals with T1D may be identified and red-flagged to be assessed further for sIgAD. Therefore, the individuals identified with sIgAD can be subjected to appropriate treatments before vaccination, such as vitamin A supplementation to induce the production of

sIgA. This strategy may be useful in improving and assessing cholera vaccine efficacy.

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