REVIEW ARTICLE

INVESTIGACIÓN en DISCAPACIDAD

Vol. 10, No. 1
January-April 2024
pp 42-53

doi: 10.35366/113829

Analysis of Fas gene as the causative molecule of systemic lupus erythematosus in patients with IgA vasculitis (Henoch-Schönlein purpura)

Análisis del gen Fas como molécula causante del lupus eritematoso sistémico en pacientes con vasculitis IgA (púrpura de Henoch-Schönlein)

Adrián Daniel Doníz-Viveros,* Michelle Copca-Barrientos,*
Pablo Shamash Hernández-Uribe,* Jorge Vidar Antonio Ortega-Espinosa*

Keywords:
IgA vasculitis, systemic lupus erythematosus, Fas, apoptosis, lymphoproliferative syndrome.

Palabras clave:
vasculitis IgA, lupus eritematoso sistémico, Fas, apoptosis, síndrome linfoproliferativo.

Abstract

IgA vasculitis (HSP) and systemic lupus erythematosus (SLE) are both immune diseases that could be more interrelated than currently thought. HSP is an immune disease characterized by systemic small vessel vasculitis and mesangial deposits of immunoglobulin A, which ultimately leads to failure in apoptotic clearance and to the generation of a chronic lymphoproliferative syndrome. SLE is an immune disease characterized by chronic systemic inflammation that affects multiple tissues and systems, and its origin lies in the formation of double-stranded anti-DNA antibodies, which in turn are generated by failures in apoptotic clearance. HSP can be considered as a triggering factor for the development of systemic lupus erythematosus probably as the result of alterations in the apoptotic clearance that we think could be related to the inhibition of non-coding long-chain RNA genes (ENST00000378432, ENST00000571370, uc001kfc.1 y uc010qna.2) in patients with HSP, that in consequence alters Fas gene (CD95) track and the functions of the tumor necrosis factor family, that in turn inhibits the secretion of phosphatidylserine which ultimately generates a lymphoproliferative syndrome which possibly activates the double-stranded anti-DNA antibodies, the origin of SLE.

Resumen

La vasculitis IgA (HSP, por sus siglas en inglés) y el lupus eritematoso sistémico (SLE, por sus siglas en inglés) son enfermedades inmunológicas que podrían estar más interrelacionadas de lo que se piensa. La HSP es una enfermedad caracterizada por vasculitis sistémica de pequeños vasos y depósitos mesangiales de inmunoglobulina A, lo que conduce a fallas en el aclaramiento apoptótico y a la generación de un síndrome linfoproliferativo crónico. El SLE es una enfermedad caracterizada por una inflamación sistémica crónica que afecta múltiples órganos y sistemas, su origen radica en la formación de anticuerpos anti-DNA de doble cadena, que también son generados por fallas en el aclaramiento apoptótico. La HSP puede considerarse como un factor desencadenante de SLE, probablemente como resultado de alteraciones en el aclaramiento apoptótico, que podría estar relacionado con la inhibición de genes de ARN de cadena larga no codificante (ENST00000378432, ENST00000571370, uc001kfc.1 y uc010qna.2) en pacientes con HSP, que en consecuencia alteran el gen Fas (CD95), así como la función del factor de necrosis tumoral que a su vez inhibe la secreción de fosfatidilserina, lo que activaría los anticuerpos anti-DNA de doble cadena, el origen del SLE.

* Department of Basic Investigation at Facultad Mexicana de Medicina at Universidad La Salle.

Correspondence:
Michelle Copca-Barrientos
E-mail: michellecopk@gmail.com

Received: June 20, 2023
Accepted: November 9, 2023

How to cite: Doníz-Viveros AD, Copca-Barrientos M, Hernández-Uribe PS, Ortega-Espinosa JVA. Analysis of Fas gene as the causative molecule of systemic lupus erythematosus in patients with IgA vasculitis (Henoch-Schönlein purpura). Invest Discapacidad. 2024; 10 (1): 42-53. https://dx.doi.org/10.35366/113829

METHODOLOGY

This article is organized in the form of a narrative review. The decision to adopt this approach was made after carefully evaluating the existing literature and considering a well-defined research question (the identification of the Fas gene as the causative molecule of systemic lupus erythematosus in patients with IgA vasculitis). This choice was reinforced by a thorough critical analysis, which involved summarizing the qualitative evidence and employing a reproducible search strategy. Furthermore, the selection of relevant studies and extraction of data were executed with rigorous precision.

Literature search platforms: PubMed: each pathology was examined within a nonspecific timeframe and organized by relevance, without specifying the language. Each individual pathology was examined both with and without captions that identify a molecular pathway involving the FAS gene. Additionally, articles that demonstrate established correlations between systemic lupus erythematosus and IgA vasculitis in patients were reviewed. This research was characterized by its heterogeneity from start to finish. Google Scholar was utilized, along with the inclusion of full text and associated data. Furthermore, Scopus was employed, with a subject area filter for medicine, immunology and microbiology, biochemistry, genetics, and molecular biology. The keywords Fas, systemic lupus erythematosus, IgA vasculitis, and Henoch Schönlein Purpura were marked. Other resources such as Web of Science, ScienceDirect, and PubMed Central were also consulted.

The time period covered was from 1982 (Lippman SM, Lockard Conley C, Ness PM, Meyers DA, Bias WB. Genetic Factors Predisposing to Autoimmune Diseases Autoimmune Hemolytic Anemia, Chronic Thrombocytopenic Purpura, and Systemic Lupus Erythematosus. Am J Med. 1982;73:827-840 to 2023) to 2023 (Amy Paskiewicz, Jianli Niu, Christopher Chang. Autoimmune lymphoproliferative syndrome: A disorder of immune dysregulation Autoimmun Rev. 2023 Sep 6;103442).

Limitations in the methodology: only a single article investigates explicitly the apparent correlation involving HSP and juvenile SLE at a clinical magnitude, thus potentially lacking representativeness of the overall population.

Limitations in the research: the absence of research that illustrates the molecular pathways linking both entities is a notable deficiency. Consequently, this inadequacy presents an opportunity for an initial exploratory investigation, enabling the identification of gaps in this field. The studies included in this analysis exhibit variations in terms of methodology, the population under investigation, research design, and other pertinent aspects. Consequently, this heterogeneity hinders comparison and synthesis. In order to comprehend the relationship between both diseases beyond the mere clinical interconnection points, as suggested by the article, it is essential to conduct future experimental studies. These investigations will offer an elucidation of the connection between the two diseases.

INTRODUCTION

The evolution of one autoimmune entity to another autoimmune disease has been extensively examined over the past few decades. One particular case that has experienced significant advancements in recent years is the transition from undifferentiated connective tissue diseases (UCTD) to well-defined connective tissue diseases (CTD).[1-4]

UCTDs are a collection of diseases that lack conformity with the established classifications for clinical diagnosis, such as those formulated by the American College of Rheumatology. These diseases exhibit overlapping clinical features, like incomplete forms of systemic lupus erythematosus (SLE). On the other hand, well-defined CTDs encompass a heterogeneous group of diseases that demonstrate a clear alignment with certain established and universally accepted clinical characteristics.[1-4]

A cohort study conducted by the Rheumatology Unit at the University of Pisa in 2013 revealed that 36% of 83 patients with UCTD, who were undergoing treatment, progressed to CTD. At the beginning of the study, all participants displayed clinical manifestations that qualified as stable UCTD, including joint involvement, Raynaud's phenomenon, leukopenia, and thrombocytopenia. Later, among the 30 patients whose disease evolved into defined CTD, 22 were identified as SLE, 3 as primary Sjögren's syndrome (pSS), 3 as rheumatoid arthritis (RA), 1 as systemic sclerosis (SSc), and 1 as mixed connective tissue disease (MTCD).[3]

Another study, published in 2022, conducted a systematic review and meta-analysis to establish the predictive value of both clinical and laboratory parameters in the progression from UCTD to CTD. This was particularly focused on diseases such as SLE

and SSc. The review encompassed the examination of relevant publications utilizing databases such as MEDLINE, EMBASE, and the Cochrane Central Register of Randomized Controlled Trials. Only studies that met specific criteria, including a minimum of 20 UCTD cases, a minimum follow-up period of 6 months, and at least one risk factor for developing CTD, were selected. A total of 59 studies were included in the systematic review, while 41 were utilized in the meta-analysis. The findings indicated that factors such as age, the presence of specific antibodies, and various components of the autoimmune system, including proinflammatory cytokines and HLA molecules, exhibited predictive patterns for the progression of UCTD to CTD.[4]

The comprehension of the shift from undifferentiated connective tissue disease (UCTD) to connective tissue disease (CTD) is crucial due to its contribution in establishing the theoretical framework for the behavior of autoimmune diseases. The transitions between these two conditions offer a promising avenue of investigation for the early detection and intervention of individuals who are susceptible to their development.

Another known example of the evolution of one autoimmune entity to another autoimmune disease has occurred in patients with immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA) that evolved to SLE years later. The relationship between these diseases is well established. ITP and AIHA are types of thrombotic microangiopathic (TMA) syndromes, which are commonly found in patients with SLE. While ITP and AIHA typically occur after the manifestation of SLE, there are cases where they occur earlier and precede the onset of SLE. The lack of tolerance to autoantibodies is the underlying cause of both ITP and AIHA in patients with SLE, leading to the destruction of erythrocytes, cell death, and a progressive decrease in platelets.[5-8]

Hematological manifestations are commonly observed in patients with SLE, but the nature of these manifestations varies greatly depending on the individual characteristics of each patient. This is why recent research has focused on identifying specific molecular (genetic) patterns that can enable a more personalized approach to diagnosis and treatment. For instance, in childhood-onset systemic lupus erythematosus (cSLE), hematological manifestations may be the initial presentation of the disease, which can be more severe in this age group. Approximately 25% of childhood SLE patients exhibit these hematological phenomena. Comparisons between cSLE and adult-onset SLE (aSLE) have revealed that children with AIHA and ITP have a higher prevalence of constitutional symptoms such as fever, weight loss, hepatosplenomegaly, and low levels of hemoglobin.[5-8]

In a 2016 case report, a 34-year-old female patient presented with thrombocytopenia, hemolytic anemia, and schistocytes in the peripheral smear. Shortly after, she developed SLE, meeting the diagnostic criteria set by the systemic Lupus International Collaborating Clinics (SLICC). This poses a challenge in terms of treatment, as there are established guidelines for managing patients who have SLE and subsequently develop ITP and AIHA, but the same does not apply to patients who initially have ITP and AIHA and then develop SLE.[5]

This paper explores the connection between two immune disorders, IgA vasculitis (HSP) and systemic lupus erythematosus (SLE), which may have more interdependence than previously recognized. Failure in apoptotic clearance and lymphoproliferative syndrome are common features in both diseases. HSP is an immune disorder characterized by systemic vasculitis and the presence of deposits of IgG anti-GalNAc-IgA1 in the mesangium. These deposits are complexes formed by Galactose-Deficient IgA1 (predominant subclass of immunoglobulin in the serum), and the IgG that is targeting them. The aforementioned occurrence results in the advancement of progressive nephritis, failure in apoptotic clearance and the emergence of chronic lymphoproliferative syndrome.[9-11] SLE is a chronic immune disease that results from the formation of anti-DNA antibodies due to apoptotic clearance failure, leading to systemic inflammation in multiple tissues and systems.[10-17]

A positive association between HSP and juvenile SLE was reported in a case-control study. The investigators identified particular risk factors based on information obtained from a systematic review, including childhood age of approximately 10 years, female sex, and anemia. Specifically, advanced age and decreased levels of hemoglobin were found to be associated with increased odds ratios of 1.37 (with a 95% confidence interval of 1.06 to 1.89) and 5.39 (with a 95% confidence interval of 2.69 to 15.25), respectively. The molecular point of union between the two diseases cannot be determined by the researchers. However, a molecular deficiency in the apoptotic clearance pathway is likely involved, and future experimental studies are needed to explain how both diseases are related beyond the clinical interconnection points, as suggested by the article. Finally, considering its retrospective nature, the article possesses certain limitations. The primary bias that arises is the inclusion bias, despite the limited available

information regarding the subject matter. Moreover, the number of participants of this study is another potential source of bias. Throughout the duration of this study, the cases were assessed by the respective Departments of Rheumatology and Immunology; however, the precise number of rheumatologists who confirmed both diagnoses remains undisclosed.[18]

Apoptosis, a biological process of cell death, is characterized by three stages: stimuli, pathways, and effector mechanisms that execute the death program.[13-15] The apoptotic process being deficient in autoimmune diseases like SLE and HSP causes the perpetuation of the lymphoproliferative syndrome and the inability of the organism to eliminate it.[13-17]

In the pathogenesis of systemic lupus erythematosus and IgA vasculitis there is a common pathway that is increased, the FAS/FAS ligand (FASL) pathway, however in both diseases there are mutations that interfere with its function. Fas and FasL are cell surface molecules that play an important role in apoptosis. It has been observed that in patients with IgA vasculitis there is an increase in the expression of these molecules in neutrophils and lymphocytes.[11]

The participation of FAS has also been demonstrated in the pathogenesis of SLE, and it has been observed that mutations in Fas or FasL contribute to deficient apoptosis, which leads to the appearance or maintenance of lymphoproliferative syndrome.[19]

This manuscript examines the contribution of the Fas protein to the apoptotic pathways associated with autoimmune disorders, namely HSP and SLE. Fas protein is an essential mediator in the extrinsic process of apoptosis, which undergoes modifications in these illnesses. The successful execution of each stage in the appropriate sequence is critical for attaining optimal apoptotic physiology. Fas, also known as CD95, is a molecule that plays a crucial role in the process of apoptosis, or programmed cell death. It is involved in the recognition and removal of apoptotic cells. In the context of the research paper, Fas is important because we believe it is the causative molecule of Systemic Lupus Erythematosus (SLE) in patients with IgA vasculitis (HSP). Alterations in the apoptotic clearance pathway, possibly related to the inhibition of non-coding long-chain RNA genes, can lead to the inhibition of the Fas gene track and the functions of the Tumor Necrosis Factor Family, ultimately generating a lymphoproliferative syndrome which possibly activates the double-stranded anti-DNA antibodies, the origin of SLE.[10-30]

Although there is not enough research at the molecular level to establish a definitive connection between the two diseases, examination of each individual aid and its pathophysiological patterns may offer a more lucid understanding of how these processes might develop.

IGA VASCULITIS (HSP)

HSP is an autoimmune disease that predominantly affects children and is characterized by vasculitis. The pathophysiology of HSP involves the development of IgA-mediated autoimmune hypersensitivity vasculitis. This condition can impact various organs such as the kidneys, joints, skin, and gastrointestinal tract. The formation of IgA-antibody immune complexes that accumulate in the blood vessels and mesangial cells is a hallmark of HSP. These complexes are a result of the abnormal glycosylation of IgA1 and the subsequent production and misidentification of galactose-deficient IgA by IgG.[10]

Most organic manifestations of HSP are limited in nature, but renal involvement, particularly nephritis, is frequently observed, leading to gradual renal damage and ultimately resulting in renal failure. HSP-associated nephritis is primarily caused by anomalous glycosylation of IgA1, which lacks galactose. This is because of the absence of B1-galactosyl residues in the hinge region of IgA1, which triggers the formation of IgA that is deficient in galactose. As a result of galactose deficiency, N-acetylgalactosamine groups are exposed in the hinge region of IgA1.[10]

Anti-IgG or anti-IgA1 antibodies recognize these epitopes and lead to an immune complex formation by two principal mechanisms:

1. During the process of circulation is generated and afterward settled onto the glomerular basal membrane.[10]
2. The basal membrane of the glomerulus is synthesized locally after the deposition of IgA that is deficient in galactose.[10]

The deposition of immune complexes within the glomerular basement membrane, irrespective of the underlying mechanism, induces the activation of the complement system, specifically the lectin and alternative pathways, the primary purpose of which is to eliminate these immune deposits. Nevertheless, in certain instances, this process results in mesangial inflammation and subsequent nephritis in patients.[10] In a similar vein, there exist certain instances where a failure in apoptotic clearance may be triggered, leading to the activation of lymphoproliferative syndrome.[11]

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

SLE is a form of autoimmune disorder that has a multifaceted origin and numerous etiologies. The disease is primarily characterized by persistent systemic inflammation, which can affect multiple tissues and organ systems. This type of inflammation is mainly triggered by the formation of double-stranded anti-DNA and antinuclear antibodies, which arise due to an error in the apoptotic clearance process. These antibodies are responsible for inducing an immune response against endogenous nuclear material, resulting in damage to multiple organs and tissues, such as the skin, kidneys, and blood vessels.[12]

Before delving into further details, it is significant to differentiate the timing of the emergence of defects in apoptotic clearance between SLE and HSP, with HSP showing such occurrence only after the ailment has fully progressed,[10] while in SLE, it is one of the principal factors that activate the disease.[12] Understanding the failure in apoptotic clearance is crucial in preventing the development of SLE in patients with HSP and potentially connecting both diseases through lymphoproliferative syndrome.[13-15]

Lupic nephritis, resulting from an inflammatory response to immunogenic chromatin containing oxidized mitochondrial DNA and apoptosis-derived microvesicles, is a common and severe complication of SLE,[17] it may be valuable to investigate the potential correlation between increased susceptibility to developing certain consequences and the occurrence of SLE after having had HSP among patients.

HSP AS A RISK FACTOR TO DEVELOP SLE

In 2019, a case-control study was conducted which demonstrated a positive correlation between two diseases, namely HPS and juvenile SLE. The researchers concluded that HPS acts as a risk factor for the development of juvenile SLE. Before conducting any specific study, the researchers discovered 15 children with juvenile SLE who had previously suffered from HSP *(Table 1)*. The researchers noted that this relationship was not documented in any literature. Therefore, they conducted a systematic review to identify the age range in which HSP is more prevalent. Subsequently, they exposed the potential prognostic factors that exist between the two diseases through a case-control study. The researchers collected data from 110 children with HSP who attended the Instituto Nacional de Pediatría.[18]

Based on the information obtained from the systematic review, the investigators found that 12,819 subjects with HSP and 110 controls were exposed to particular risk factors, including a childhood age of approximately 10 years, female sex, and anemia. The study identified older age and lower hemoglobin levels as prognostic factors, with respective odds ratios of 1.37 [1.06, 1.89] and 5.39 [2.69, 15.25]; however, they could not determine the molecular point of union between both diseases.[18]

In this study based on case-control analysis, the primary article under review emphasized the necessity of conducting experimental research to elucidate the association between the two diseases beyond their clinical interconnection. Nonetheless, the article asserts that a molecular insufficiency in the apoptotic clearance pathway is plausibly a pathophysiological occurrence for which we aim to furnish a response, given the extant literature.[18]

APOPTOSIS

Apoptosis is a process that has been extensively studied in various autoimmune diseases, with particular attention given to SLE and HSP due to their high occurrence and significance. Apoptosis is a natural cellular mechanism of programmed cell death that takes place in multicellular organisms. The stages of apoptosis include the stimuli that induce cell death, the pathway through which the message is relayed to the cell, and the effector mechanisms that carry out the death program.[14]

Different types of stimuli can activate a cellular response that leads to programmed cell death, or apoptosis. Despite the variety of stimuli that can initiate apoptosis, the pathways eventually converge on the same effector mechanisms. During this stage of the process, the family of cysteine proteases, particularly caspases, plays a key role. These endoproteases provide critical connections within the cell regulatory system, ultimately controlling inflammation and apoptosis. Upon activation by the stimuli, cysteine proteases directly or indirectly cause morphological and biochemical alterations that are characteristic of apoptosis.[13-15]

Apoptosis in SLE

The efficient phagocytosis of apoptotic cells by specific neighboring cells such as macrophages is a physiological phenomenon referred to as apoptotic clearance. This process has been identified as one of the most dysregulated and significant contributors

Table 1: Presents the principal clinical and laboratory characteristics of patients diagnosed with IgA vasculitis (HSP) who subsequently developed juvenile systemic lupus erythematosus (jSLE).[18]

Patient	Year old	Sex	
1	9	Male	IgA vasculitis with onset at the age of 9 years and 7 months, which later (3 months) progressed to jSLE, with the presence of nephritis, haemolytic anemia, serositis and lymphopenia
2	14	Female	IgA vasculitis onset with petechiae at the age of 14 years and 4 months, evolving to jSLE at 15 years and 2 months, with malar rash, photosensitivity, oral ulcers, arthritis, nephritis and lymphopenia
3	3	Female	IgA vasculitis with onset at the age of 3 years and 3 months, progressing to jSLE three months later, with the presence of arthritis, nephritis, serositis and haemolytic anemia
4	12	Female	IgA vasculitis with angina Ecchymos with onset at 12 years and 4 months of age, progressing to jSLE two months later, with the presence of arthritis and nephritis
5	9	Female	IgA vasculitis with onset at the age of 9 years and 11 months evolving to jSLE at the age of 10 years and one month, including the presence of malar rash, photosensitivity, oral ulcers, arthritis, nephritis, haemolytic anemia and lymphopenia
6	13	Female	IgA vasculitis with onset at 13 years and 7 months of age, progressing to jSLE by the age of 14 years, including the presence of malar rash, oral ulcers, arthritis, nephritis, serositis, haemolytic anemia and lymphopenia
7	12	Female	IgA vasculitis with onset at 12 years and 5 months of age that progresses to jSLE at 12 years and 7 months of age, with the presence of arthritis, nephritis, haemolytic anemia and lymphopenia
8	13	Female	IgA vasculitis with onset at 13 years and 2 months, progressing to jSLE at 13 years and 5 months of age, with the presence of nephritis and malar rash
9	9	Female	IgA vasculitis with an onset at 9 years and 11 months, progressing to jSLE at 11 years and 7 months of age, with the presence of malar rash, photosensitivity, arthritis and nephritis
10	11	Male	IgA vasculitis with an onset at 11 years and 11 months, progressing to jSLE at 12 years and 2 months with the presence of arthritis, nephritis, and lymphopenia
11	9	Male	IgA vasculitis with an onset at 9 years and 9 months, progressing to jSLE at 10 years and 1 month with the presence of arthritis, nephritis, hemolytic anemia and lymphopenia
12	10	Female	IgA vasculitis with an onset at 10 years and 7 months, progressing to jSLE at 12 years with the presence of malar rash, oral ulcers, arthritis, nephritis and lymphopenia
13	6	Female	IgA vasculitis with an onset at 6 years and 3 months, progressing to jSLE at 6 years and 7 months, with the presence of arthritis, nephritis and lymphopenia
14	5	Female	IgA vasculitis with an onset at 5 years and 2 months, progressing to jSLE at 7 years, with the presence of malar rash, oral ulcers, arthritis, nephritis, hemolytic anemia and lymphopenia
15	14	Female	IgA vasculitis with an onset at 14 years, which later (3 months) progressed to jSLE, with the presence of arthritis, nephritis and lymphopenia

to the pathophysiology of SLE. In cases where the apoptotic clearance process fails, the accumulation of Damage-Associated Molecular Patterns (DAMPs) occurs over time. The body's inability to eliminate these DAMPs stimulates the immune system, leading to the development of a lymphoproliferative syndrome characterized by the presence of double-stranded anti-DNA and antinuclear antibodies[15] *(Figure 1)*.

In SLE, the normal process of apoptosis is hyperactivated, resulting in the accumulation of physiological residues throughout the body due to inefficient apoptotic clearance. This phenomenon has a significant impact on cell selection, leading to the selection of cells that are not qualified for submission to the process. As a result of this disorganized and massive selection and impaired apoptotic signaling, macrophages fail to reach the site to phagocytose cellular debris. This pathophysiological occurrence triggers the cell to undergo a state called 'secondary necrosis', leading to the disintegration of the apoptotic surface and exposure of vesicles containing intracellular organelles to the extracellular space, resulting in the development of self-antigens.[12-15]

Antigens of endogenous origin, which are known as self-antigens, are taken up by specialized cells, specifically dendritic cells that possess the capability to capture these nuclear antigens and subsequently present them in peptide form to the T

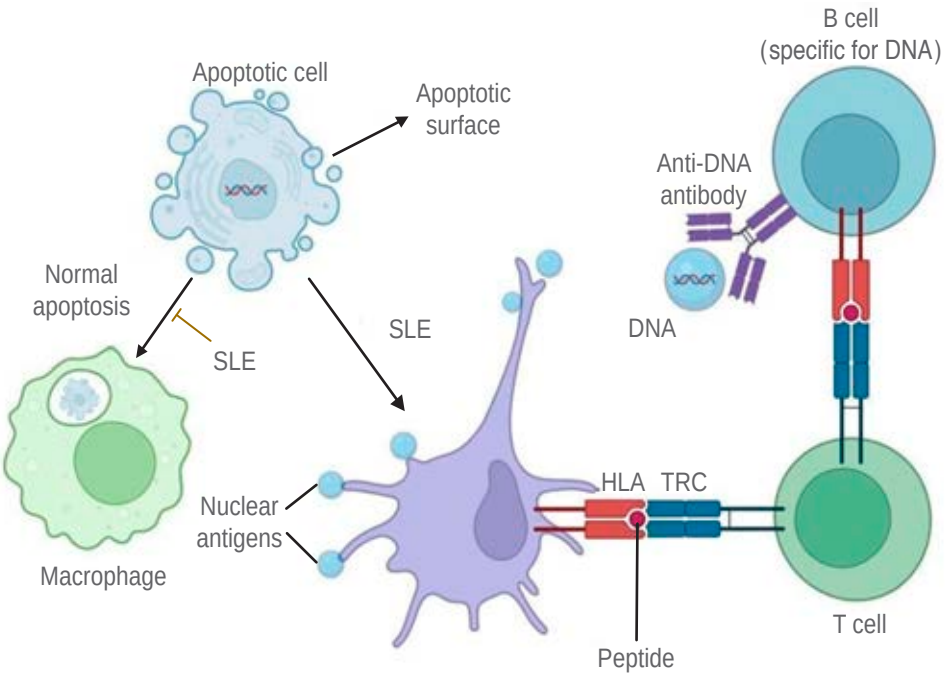

Figure 1: Physiopathology of systemic lupus erythematosus. In a proper instance of apoptosis, the cell undergoes biochemical processes that enable chromatin condensation while packaging all intracellular organelles into vesicles. This prevents organelle exposure and subsequent inflammation, as in the case of necrosis. The apoptotic cells are then efficiently phagocytosed by neighboring macrophages. However, in cases of systemic lupus erythematosus, this process is disrupted, leading to the exposure of intracellular elements and DAMPs. This triggers the activation of the autoimmune system and the eventual production of double-stranded anti-DNA and antinuclear antibodies.[15]

and B lymphocytes.[14] B lymphocytes are accountable for the synthesis of antinuclear antibodies, precisely those of double-stranded anti-DNA antibodies, which are the causative agents of harm inflicted upon cells and tissues.[12]

The autoimmune lymphocytes display a unique characteristic of the reduced apoptotic process, which is in stark contrast to other cells within the organism. This creates a paradoxical effect wherein the autoimmune lymphocytes continue to persist and the organism is unable to eliminate them.[13-15]

Apoptosis in HSP

As previously mentioned, the lack of successful apoptotic clearance in HSP occurs once the ailment has established and progressed. This process initiates with the presence of antigens that can penetrate a compromised intestinal mucosa. Subsequently, the entry of these antigens triggers the immunological activation of IgA, which in HSP patients is characterized by being Galactose-deficient IgA (Gd-IgA1). Due to this defect, the residues known as GaINAc are exposed, which the body attempts to eliminate by attacking them with IgG anti-GaINAC IgA immunoglobulins, ultimately leading to the formation of immunocomplexes. These complexes have a predilection to settle in the endothelium of the renal glomerulus, which stimulates the activation of an inflammation cascade at the glomerular level, generating nephritis. It has been observed that in some patients, the accumulation of these complexes in the renal glomerulus results in the development of lymphoproliferative syndrome when self-reactive B lymphocytes are activated. This physiopathological phenomenon is a consequence of a previous failure in apoptotic clearance that cannot remove them[10] *(Figure 2)*.

FAS AND APOPTOSIS

Up until this juncture, it has come to our attention that HSP and SLE are two autoimmune diseases that bear

a commonality in the form of the deficiency in apoptotic clearance and lymphoproliferative syndrome,[10,12,16,17] from this point forward, we will clarify that the pathophysiological stages may potentially originate from the disturbance of a unique molecular pathway related to a gene that encodes a protein, specifically Fas (cell surface death receptor), which plays an essential role in apoptotic mechanisms.

Apoptosis, a programmed cell death mechanism, is instigated through two pathways, intrinsic and extrinsic. The former pathway is triggered by intracellular imbalances arising from exposure to hazardous agents or damage to the DNA, resulting in the permeabilization of the mitochondrial membrane as well the liberation of cytochrome c, which ultimately activates caspase 3. On the other hand, the extrinsic pathway is activated by cell death receptors that are found on the surface of the cell, such as Fas and CD95, which upon binding to their respective ligands, promote membrane oligomerization and the generation of platforms in the cell that activate adaptor proteins (TRADD and FADD) leading to the activation of caspases 8 and 10, culminating in a complex signaling pathway for cell death (DISC). It is noteworthy that the absence of caspase 8 activation precludes necrosis, underscoring the significance of the sequential execution of these phases to ensure optimal physiology of apoptosis.[14]

The level of complexity inherent in Fas is influenced by its origin and location, with a substantial number of physiopathological indications suggesting that it can interact and act as a causative factor. Fas is a crucial participant in the process of apoptosis and is a member of the tumor necrosis factor (TNF) family, which is triggered by p53. Additionally, Fas is widely spread throughout various locations, with particular prevalence in the thymus, liver, heart, kidney, T, and B lymphocytes, and central nervous system cells.[14]

In 2019, research was conducted that established that patients with nephritis due to HSP showed a decrease in the expression of genes ENST00000378432, ENST00000571370, uc001kfc.1, and uc010qna.2, which are associated with p53 signaling. These genes play a pivotal role in the assembly of the autoimmune response, and their deregulation can lead to the deregulation of the Fas ligand and subsequent processes. The study highlights the importance of these long-chain non-coding RNA molecules in regulating the activity of the

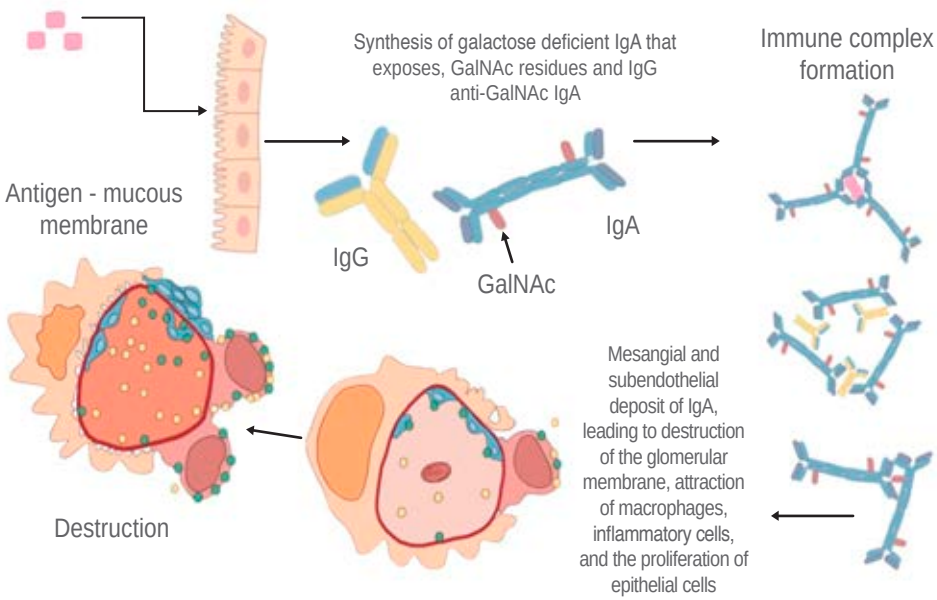

Figure 2: Pathophysiology of HSP. Genetic and epigenetic elements are involved in the activation of the mucosal immune system following exposure to antigens. This results in a heightened penetration of antigens due to compromised mucosal immunity. The antigens then arrive at the mucosa-associated lymphoid tissue and instigate the activation of dendritic cells and CD4+ T lymphocytes, culminating in the production of GalNAc-IgA1 and subsequent generation of IgG anti-GalNAc-IgA1 autoantibodies. The deposition of circulating immune complexes of IgG anti-GalNAc-IgA1 in subendothelial and mesangial regions leads to the formation of fibrin in the presence of macrophages and inflammatory cells, thereby destroying the glomerular basement membrane posteriorly.[10]

TNF family.[18,26] The identification of the deleterious impact of these genetic functions might prove to be a crucial factor in timely intervention and prevention of systemic lupus erythematosus in patients with hereditary spastic paraplegia. Nevertheless, further research is warranted, as acknowledged by the authors. Among the techniques employed in this investigation were RNA isolation, pathway scrutiny, RT-qPCR confirmation, and statistical evaluation.[20]

Once the Fas pathway was altered, either by alterations in itself or by alterations in TNF or p53, we found the following effects:

1. Over apoptotic activation

When the pathway of Fas experiences a malfunction, a range of outcomes can be observed, including the over-activation of apoptosis. Such molecular deregulation can be found in all cells where Fas is present, leading to the selection of cells that do not meet the requirements for this process, except for lymphocytes.[14] In this particular instance, the aforementioned pathophysiological impact initiates an undetermined quantity of cells to undergo the process of apoptosis, despite not meeting the necessary criteria for such a response.[22]

We have designated the ensuing three investigations to unveil the extensive regulatory role of Fas within the organism, specifically the over-activation of Fas in patients afflicted with diverse immune disorders, highlighting the potential for varied etiologies of its deregulation, including genetic etiology.[12]

The findings of a study that was published in the year 2019 indicate an escalated activity of Fas in subjects who suffer from SLE. This was determined by investigating the regulation of the survival of innate lymphoid cells (ILCs) belonging to groups 2 and 3 through overexpression of Fas. The data of SLE patients was scrutinized through flow cytometry in this research.[21]

In 2020, a separate investigation revealed that subjects suffering from systemic lupus erythematosus (SLE), particularly those with renal impairment, exhibit augmented existence of the Fas ligand as determined by enzyme-linked immunosorbent assay (ELISA). This has led to the conclusion that the elevated presence of the ligand is associated with the presence of SLE, and, to a lesser extent, linked to direct organ damage.[22]

In a study that was published in 2012, it was observed that patients with SLE exhibited an increase in the activity of the Fas ligand at the peripheral level, which was specifically identified through single nucleotide polymorphisms. To detect the allelic and genotypic frequencies of these SNPs in a certain number of patients with and without SLE, a case-control study was conducted.[23]

2. Failure of apoptotic clearance due to inhibition of phosphatidylserine and chemokines secretion

Phosphatidylserine plays a pivotal role in facilitating the apoptotic processes by identifying the cellular residues that require elimination. Nonetheless, the deregulation of Fas inhibits the secretion of phosphatidylserine along with other crucial molecules, thereby rendering the cells that have undergone apoptosis unremovable.[24] We selected the following articles to expose this key function of Fas in apoptotic clearance.

In 2016, a review was conducted which revealed that in HeLa cells, the induction of apoptosis via Fas or CD95 resulted in the discharge of the chemokines MCP-1 and IL-8, both acknowledged as myeloid/phagocytic chemoreactants. Consequently, the contribution of Fas in this segment of the apoptotic process is progressively merged into the investigations.[25]

A recent review carried out in the year 2021 has brought to light that chemokines that have been traditionally recognized, namely IL-8 and MCP1, are released by Fas and play a direct role in facilitating the movement of phagocytes such as macrophages towards cells that are undergoing apoptosis or dying.[26]

In 2002, a study was conducted that demonstrated the direct involvement of the ligand Fas in the crucial process of phosphatidylserine recognition and removal of apoptotic cells. This was accomplished through the application of diverse techniques, including phagocytosis, lipid peroxidation, externalized phosphatidylserine detection via fluorescence marking, and phosphatidylethanolamine.[24]

3. Generation of DAMPs

When Fas becomes deregulated, it has been observed that it can result in not only the failure of apoptotic clearance but also the release of DAMPs. This occurs because Fas induces apoptosis in cells that are not intended for this process, and subsequently, the removal of these cells is prevented. These key issues activate an adaptive self-reactive immunity reaction which can result in damage to multiple organs and ultimately lead to the development of chronic lymphoproliferative syndrome.[12-14]

4. Generation and maintenance of lymphoproliferative syndrome as a result of the inhibition of its process in T and B

Fas is found in both T and B lymphocytes and serves as a pathway for apoptosis and subsequent clearance.[14]

It has been established that the Fas pathway's compromised functionality leads to the development of lymphoproliferative syndrome due to excessive DAMPs and self-tolerance loss. However, Fas is not hyperactivated but rather downregulated in autoreactive lymphocytes, indicating their inability to be eliminated. In summary, Fas deregulation plays a crucial role in the onset and persistence of lymphoproliferative syndrome.[12-15] The clinical manifestations of lymphoproliferative syndrome triggered by Fas malfunction encompass the existence of adenopathy, splenomegaly, and cytopenias in the pediatric population.[16]

In the year 2013, research was carried out which revealed that Fas modifications led to a rise in the ratio of activation in a majority of cells where it is present; nevertheless, as mentioned earlier, it is reduced in both T lymphocytes and B lymphocytes. This implies that excessive lymphoid proliferation cannot be subjected to appropriate apoptosis and subsequent physiological clearance, leading to the perpetuation of lymphoproliferative syndrome over time and its progression into a chronic condition. The techniques employed in this study encompassed DNA isolation and sequencing, apoptosis tests, RNA isolation, and cDNA synthesis.[27]

In 2015, a separate investigation was carried out which revealed that ILI2RB1 and IL12 signaling pathways exhibit a propensity for triggering lymphoproliferative syndrome owing to their inherent association with Fas expression. In this study, DNA was extracted.[28]

In 2014, a research study was conducted which demonstrated that an overabundance of the Fas antigen can result in excessive apoptosis of bone marrow hematopoietic cells, leading to the development of severe aplastic anemia. The study utilized flow cytometry techniques, as previously outlined, to investigate this phenomenon.[29]

In 2018, a study was conducted that revealed the indispensable involvement of Fas in the apoptotic mechanisms observed in hematopoietic cells. Moreover, it was found that the interdependence between the incidence of idiopathic aplastic anemia and the expression of Fas necessitates a thorough analysis. The study employed Tetra-ARMS polymerase chain reaction to genotype DNA samples obtained from the study participants.[30]

FAS AS THE UNION FACTOR BETWEEN SLE AND HSP

The relationship between Fas deregulation and autoimmune diseases is significant.[18-28] Hence, it comes as no surprise that current research has established the existence of a connection between Fas and these ailments that goes beyond mere theoretical correspondences. This development is aimed at achieving earlier detection and novel treatment approaches.

The relationship that demands our attention is the connection that exists between HSP and SLE, owing to its possible significance.[17] The pathologies that exhibit the aforementioned deficiencies resulting from Fas deregulation, and additionally, owing to their chronic development, it is highly probable that we are confronting the etiology of these associations[18-27] *(Figure 3)*. We encountered a situation in the realm of medical literature where we were in unfamiliar territory. We were presented with a molecular pathway that, if validated by a future experimental method, would provide a novel paradigm for identifying alternative means of diagnosis and treatment.

The diseases HSP and SLE have been observed to intersect at different levels, but by analyzing the pathophysiological outcomes resulting from deficiencies in the molecular pathway of Fas, it appears highly probable that this particular molecule, in conjunction with other factors, contributes to the increased risk of developing SLE in individuals with HSP.

CONCLUSIONS

The research paper presents findings that demonstrate a potential link between IgA vasculitis (HSP) and systemic lupus erythematosus (SLE) in certain patients. The study suggests that an alteration in the apoptotic clearance pathway may be responsible for this association. Specifically, it is believed that the inhibition of non-coding long-chain RNA genes may result in the inhibition of the Fas gene track and the functions of the Tumor Necrosis Factor Family. Ultimately, this leads to the generation of a lymphoproliferative syndrome that may activate the double-stranded anti-DNA antibodies responsible for the origin of SLE. The research highlights the crucial role of Fas in the apoptotic process and provides valuable insights into the molecular mechanisms that

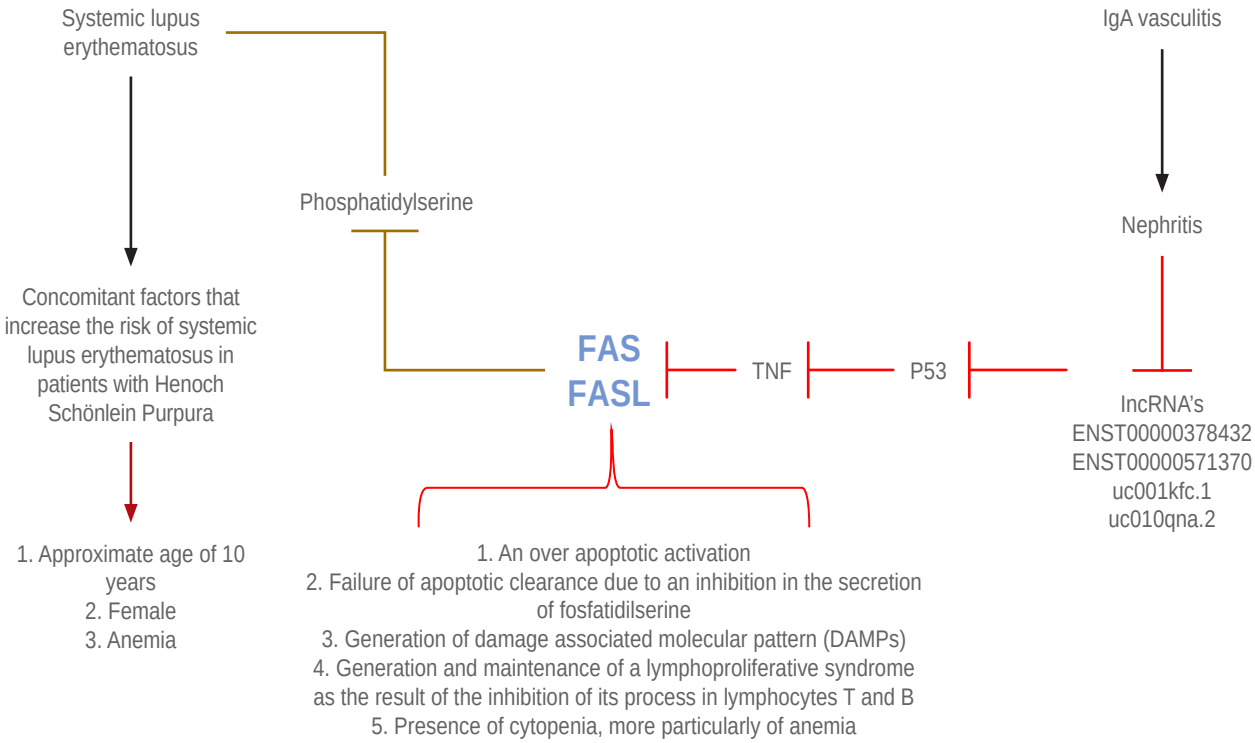

Figure 3: The downregulation of Fas in the HSP detonates systemic lupus erythematosus. Although the clinical presentation provides a clearer understanding of the risk factors that determine the development of systemic lupus erythematosus in patients with HSP, there is a lack of studies that explore the molecular level of connection between the two diseases. However, by examining each disease in isolation and following their pathophysiological patterns, it is possible to gain insight into how these processes may be linked. This proposed scheme offers a potential molecular relationship between HSP and systemic lupus erythematosus, but it should be noted that the downregulation of genes ENST00000378432, ENST00000571370, uc001kfc.1, and uc010qna.2 is not absolute, as alterations in p53 and TNF may also result in deregulation of Fas and apoptotic clearance.[16-30]

contribute to the development of immune diseases. However, further experimentation is necessary to confirm the link between HSP and SLE, and to determine the role of Fas in this association. If confirmed, this link may lead to earlier detection, novel treatment avenues, and improved quality of life for those affected by these conditions.

References

1. Mosca M, Tani C, Neri C, Baldini C, Bombardieri S. Undifferentiated connective tissue diseases (UCTD). Autoimmun Rev. 2006; 6 (1): 1-4.
2. Mosca M, Tani C, Carli L, Della Rossa A, Talarico R, Baldini C et al. Analysis of the evolution of UCTD to defined CTD after a long term follow-up. Clin Exp Rheumatol. 2013; 31 (3): 471.
3. Dyball S, Rodziewicz M, Mendoza-Pinto C, Bruce IN, Parker B. Predicting progression from undifferentiated connective tissue disease to definite connective tissue disease: a systematic review and meta-analysis. Autoimmunity Reviews. 2022; 21 (11): 103184.
4. Danieli MG, Fraticelli P, Salvi A, Gabrielli A, Danieli G. Undifferentiated connective tissue disease: natural history and evolution into definite CTD assessed in 84 patients initially diagnosed as early UCTD. Clin Rheumatol. 1998; 17 (3): 195-201.
5. Abu-Hishmeh M, Sattar A, Zarlasht F, Ramadan M, Abdel-Rahman A, Hinson S et al. Systemic lupus erythematosus presenting as refractory thrombotic thrombocytopenic purpura: a diagnostic and management challenge. A case report and concise review of the literature. Am J Case Rep. 2016; 17: 782-787.
6. Neely J, Von Scheven E. Autoimmune haemolytic anaemia and autoimmune thrombocytopenia in childhood-onset systemic lupus erythematosus: updates on pathogenesis and treatment. Curr Opin Rheumatol. 2018; 30 (5): 498-505.

7. Roussotte M, Gerfaud-Valentin M, Hot A, Audia S, Bonnotte B, Thibault T et al. Immune thrombocytopenia with clinical significance in systemic lupus erythematosus: a retrospective cohort study of 90 patients. Rheumatology (Oxford). 2022; 61 (9): 3627-3639.
8. Lippman SM, Arnett FC, Conley CL, Ness PM, Meyers DA, Bias WB. Genetic factors predisposing to autoimmune diseases. Autoimmune hemolytic anemia, chronic thrombocytopenic purpura, and systemic lupus erythematosus. Am J Med. 1982; 73 (6): 827-840.
9. Novak J, Moldoveanu Z, Renfrow MB, Yanagihara T, Suzuki H, Raska M et al. IgA nephropathy and Henoch-Schoenlein purpura nephritis: aberrant glycosylation of IgA1, formation of IgA1-containing immune complexes, and activation of mesangial cells. Contrib Nephrol. 2007; 157: 134-138.
10. Leung AKC, Barankin B, Leong KF. Henoch-Schönlein purpura in children: an updated review. Curr Pediatr Rev. 2021; 16 (4): 265-276.
11. Ozaltin F, Besbas N, Uckan D, Tuncer M, Topaloglu R, Ozen S et al. The role of apoptosis in childhood Henoch-Schonlein purpura. Clin Rheumatol. 2003; 22 (4-5): 265-267.
12. Demirkaya E, Sahin S, Romano M, Zhou Q, Aksentijevich I. New horizons in the genetic etiology of systemic lupus erythematosus and lupus-like disease: monogenic lupus and beyond. J Clin Med. 2020; 9 (3): 712.
13. Muñoz LE, Lauber K, Schiller M, Manfredi AA, Herrmann M. The role of defective clearance of apoptotic cells in systemic autoimmunity. Nat Rev Rheumatol. 2010; 6 (5): 280-289.
14. Bertheloot D, Latz E, Franklin BS. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. Cell Mol Immunol. 2021; 18 (5): 1106-1121.
15. Ekert P, Vaux D, Vaux D, Hall E. Apoptosis and the immune system. Br Med Bull. 1997; 53 (3): 591-603. doi: 10.1093/oxfordjournals.bmb.a011632.
16. Paskiewicz A, Niu J, Chang C. Autoimmune lymphoproliferative syndrome: a disorder of immune dysregulation. Autoimmun Rev. 2023; 22 (11): 103442.
17. Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C. Lupus nephritis. Nat Rev Dis Primers. 2020; 6 (1): 7.
18. Murata C, Rodríguez-Lozano AL, Hernández-Huirache HG, Martínez-Pérez M, Rincón-Arenas LA, Jiménez-Polvo EN et al. IgA vasculitis (Henoch-Schönlein purpura) as the first manifestation of juvenile systemic lupus erythematosus: case-control study and systematic review. BMC Pediatr. 2019; 19: 461.
19. Wu J, Wilson J, He J, Xiang L, Schur PH, Mountz JD. Fas ligand mutation in a patient with systemic lupus erythematosus rapid publication fas ligand mutation in a patient with systemic lupus erythematosus and lymphoproliferative disease. J. Clin Invest. 1996; 98 (5): 1107-1113.
20. Pang S, Lv J, Wang S, Yang G, Ding X, Zhang J. Differential expression of long non-coding RNA and mRNA in children with Henoch-Schönlein purpura nephritis. Exp Ther Med. 2019 Jan; 17(1): 621-632.
21. Blokland SLM, Van Den Hoogen LL, Leijten EFA, Hartgring SAY, Fritsch R, Kruize AA et al. Increased expression of Fas on group 2 and 3 innate lymphoid cells is associated with an interferon signature in systemic lupus erythematosus and Sjögren's syndrome. Rheumatology (United Kingdom). 2019; 58 (10): 1740-1745.
22. Vincent FB, Kandane-Rathnayake R, Koelmeyer R, Harris J, Hoi AY, MacKay F et al. Associations of serum soluble Fas and Fas ligand (FasL) with outcomes in systemic lupus erythematosus. Lupus Sci Med. 2020; 7 (1): e000375.
23. Lu MM, Ye QL, Feng CC, Yang J, Zhang T, Li J et al. Association of FAS gene polymorphisms with systemic lupus erythematosus: a case-control study and meta-analysis. Exp Ther Med. 2012; 4 (3): 497-502.
24. Kagan VE, Gleiss B, Tyurina YY, Tyurin VA, Elenström-Magnusson C, Liu SX et al. A role for oxidative stress in apoptosis: oxidation and externalization of phosphatidylserine is required for macrophage clearance of cells undergoing fas-mediated apoptosis. J Immunol. 2002; 169 (1): 487-499.
25. Elliott MR, Ravichandran KS. The dynamics of apoptotic cell clearance. Developmental Cell. Cell Press. 2016; 38: 147-160.
26. Han M, Ryu G, Shin SA, An J, Kim H, Park D et al. Physiological roles of apoptotic cell clearance: beyond immune functions. Life. 2021; 11 (11): 1141.
27. Magerus-Chatinet A, Stolzenberg MC, Lanzarotti N, Neven B, Daussy C, Picard C et al. Autoimmune lymphoproliferative syndrome caused by a homozygous null FAS ligand (FASLG) mutation. J Allergy Clin Immunol. 2013; 131 (2): 486-490.
28. Nabhani S, Ginzel S, Miskin H, Revel-Vilk S, Harlev D, Fleckenstein B et al. Deregulation of Fas ligand expression as a novel cause of autoimmune lymphoproliferative syndrome-like disease. Haematologica. 2015; 100 (9): 1189-1198.
29. Liu CY, Fu R, Wang HQ, Li LJ, Liu H, Guan J et al. Fas/FasL in the immune pathogenesis of severe aplastic anemia. Genet Mol Res. 2014; 13 (2): 4083-4088.
30. Rehman S, Saba N, Naz M, Ahmed P, Munir S, Sajjad S et al. Single-nucleotide polymorphisms of FAS and FASL genes and risk of idiopathic aplastic anemia. Immunol Invest. 2018; 47 (5): 484-491.