ORIGINAL ARTICLE

Annexin A1 expression in Lupus Nephritis

Expression de l'Annexine A1 dans la Néphropathie Lupique

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Abstract

Introduction: Lupus nephritis (LN) is an immune complex glomerulonephritis, caused by systemic lupus erythematosus. It is associated with an increase of morbidity and mortality. In LN, the immune responses dysregulation is one of the crucial pathogenic pathways. Annexin A1 (AnxA1), as an anti-inflammatory mediator, plays a critical role in immune responses, in addition to a variety of pathological processes.
Aim: This study aimed to evaluate the AnxA1 expression in renal tissues, in order to explore its potential role in LN pathogenesis.
Methods: AnxA1 expression was performed by immunohistochemistry staining in renal biopsies of 24 LN patients compared to 8 controls.
Results: LN patient's biopsies showed an increased distribution of AnxA1 in glomeruli compared to controls (p=0.00019). When comparing AnxA1 expression in different LN classes, a high AnxA1 intensity score was positively correlated with glomerular proliferation.
Conclusion: Our data suggest AnxA1 as a useful marker to differentiate between severe proliferative and non severe proliferative classes of LN.

Key words: Annexin A1- Immunostaining - Lupus nephritis - glomerular proliferation

Résumé

Introduction: La Néphropathie lupique (NPL) est une glomérulonéphrite à complexes immuns, provoquée par le Lupus Erythémateux. Elle est associée à une augmentation de la mortalité. Dans la NPL, la dérégulation de la réponse immunitaire est l'une des voies pathogènes. L'Annexine A1 (AnxA1), en tant que médiateur anti-inflammatoire, joue un rôle essentiel dans la réponse immunitaire, en plus de divers processus pathologiques.
Objectif : Cette étude a pour objectif d'évaluer l'expression de l'AnxA1 dans les tissus rénaux, afin d'investiguer son rôle dans la pathogenèse de la NPL.
Méthodes: l'expression de l'AnxA1 a été réalisée par marquage immunohistochimique dans des biopsies rénales de 24 patients atteints du NPL par rapport à 8 témoins.
Résultats: les patients atteints du NPL ont montré une distribution élevée de l'AnxA1 dans les glomérules par rapport des contrôles (p=0.00019). Lors de la comparaison de l'expression de l'AnxA1 dans les différentes classes du NPL, un score d'intensité élevé de l'AnxA1 a été positivement corrélé à la prolifération glomérulaire.
Conclusion: Nos données suggèrent que l'AnxA1 est un marqueur utile des classes prolifératives sévères de la NPL

Mots clés: Annexine A1, Immunomarquage, Nephropathie lupique, Prolifération glomérulaire

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Introduction

The kidney is a vital organ that performs many crucial roles including filtering blood, removing wastes, and controlling the body's fluid balance [1]. It harbors a variety of resident immune cells, which play an important role in the maintenance of the tissue homeostasis [2]. Under physiologic conditions, endothelial, epithelial, and immune cells interact harmonically within the kidney. Once activated by external or by internal events, these cells produce inflammatory mediators leading to reduce the inflammation, to repair the tissue damage, and to restore the homeostasis that could trigger a regulatory response or initiate kidney disease [2]. In addition, the kidney itself is very susceptible to immune-mediated diseases such as IgA nephropathy and membrano-proliferative glomerulonephritis [3]. Thus, it could be targeted by pathogenic immune response against renal auto antigens and/or by local manifestations of systemic autoimmunity disease like lupus nephritis (LN) [4].

LN is a frequent lupus complication (approximately 50% of lupus patients develop renal disease) [4]; it is associated with an increase of morbidity and mortality [5]. The morphologic changes in renal biopsies from patients with LN comprise a spectrum of vascular, glomerular, and tubule-interstitial lesions. Thereby, various classifications were defined for LN according to the different morphologic pattern's injury and their prognostic relevance [6]. The classification of LN has evolved over the past 40 years and each class has different prognosis and treatment [7]. Various processes such as apoptosis, necrosis and/or NETosis act abnormally in LN patients and can contribute to disease pathogenesis [8]. Inefficient clearance and accumulation of apoptotic cells generate a chronic inflammatory response and may lead to the breakdown of self-tolerance [9]. A panoply of mediators is implicated in the clearance of apoptotic cells and the resolution of the inflammatory reaction like Lipoxin A4, resolvins and Annexin A1 (AnxA1).

AnxA1 is a glucocorticoid-regulated protein with an important role in the resolution of the inflammatory reaction [10]. Indeed, AnxA1 regulates the immune cell migration to the inflammatory site, stimulates the neutrophils apoptosis in late stage of inflammation and induces the clearance of apoptotic cells by macrophages leading to tissue homeostasis [11]. AnxA1 is highly expressed in lung and nasopharynx tissues while moderately expressed in kidney and skin tissues [12]. In addition, it is more expressed by neutrophils and monocytes [13]. AnxA1 levels were modulated in many diseases including glomerulonephritis. Patients with glomerular disorders including IgA nephropathy and diabetic nephropathy showed higher expression of AnxA1 in renal tissues compared to controls. AnxA1 expression was also evaluated in LN patients by immunohistochemistry and it was found to be elevated when comparing to controls and patients presenting glomerulonephritis with minimal change [10].

Thereby, we aimed in the present research i) to explore the AnxA1 expression on renal biopsies of LN patients and control renal biopsies in the Tunisian population ii) to study the AnxA1 expression in the different classes of LN iii) to analyse the correlation of AnxA1 expression with clinical, serological and histological data of LN patients in the Tunisian population.

Methods

Patients

A total of 24 patients with LN were included in the study. Patients were followed up in the Nephrology and Internal Medicine Departments of the Hedi Chaker University Hospital of Sfax, and were diagnosed according to the International Society of Nephrology and Renal Pathology Society (ISN/RPS) classification into 6 classes (I, II, III, IV, V, VI) [7]. If there was an association of lesions of class III or IV combined with lesions of class V, the biopsy was classified as III+V or IV+V. Patients with LN class VI (were more than 90% of glomeruli present global glomerulosclerosis) and were excluded from the study. Sections containing a number of glomeruli less than 5 in H & E staining were also excluded. Clinical, serological and histological data of patients were collected at the same time of the biopsy.

Biopsies

Paraffin-embedded LN renal biopsies, fixed in Duboscq-Brasil, were collected from the Anatomopathological Department, Habib Bourguiba University Hospital, Sfax, Tunisia, for immunostaining. The biopsies were divided into 2 groups according to the proliferative status:

- Severe proliferative group: including biopsies with Class III, IV, III+V and class IV+V: G1
- Non severe proliferative group: including biopsies with class II and V: G2

As controls, 8 paraffin-embedded renal tissues, fixed in Formalin, were obtained from the normal part of the nephrectomised kidney (secondary to renal carcinoma) and cadaver kidney (autopsy) from subjects without renal disease.

Immunohistochemistry technique

Staining procedure and preparation of tissue sections were performed as described in the study of Elloumi et al [14]. For the AnxA1 detection, the anti-AnxA1 Abs [rabbit polyclonal raised against amino acids 1-100 of AnxA1 of human origin (Sigma Life Science; St. Louis, USA)] was used. For negative control preparation, section incubation was performed in the absence of the primary Ab. For positive control, we have used the interstitium infiltration with inflammatory cells as an internal positive control since AnxA1 is mainly expressed in inflammatory cells.

Semi-quantitative analysis was performed by light microscopy and the interpretation was carried out by an anatomopathologist and a nephrologist. Photographic images of representative results were captured using a Zeiss® Axiocam color camera.

Biopsy scoring

We determined three scores for each sample; distribution score, intensity score and an expression score resulting from the product: intensity score X distribution score based on the strategy adapted in the study of Elloumi et al., 2017 [14].
The Intensity Score ranged from 0 to 3: 0 for negative, 1 for weakly positive, 2 for moderately positive and 3 for strongly positive staining.
The Distribution Score ranged from 0 to 4 depending on the stained surface of glomeruli: the score was 0 for 0%, 1 for 0% to 25%, 2 for 25% to 50%, 3 for 50% to 75%, and 4 for more than 75%.
We determined also scores for fibrosis and infiltration with inflammatory cells in the interstitium of LN patients; 0 for absence, 1 for 0% to 25%, 2 for 25% to 50%, 3 for more than 50% of the interstitium.
When comparing AnxA1 expression on renal biopsies between patients and controls, we took into consideration only distribution score, since biopsies of patients and controls were fixed in different products (formol for controls and Duboscq-Brasil for patients) which can influence the staining intensity scoring [15].

Statistical analysis

Results were analyzed using SPSS version 20; the non-parametric Mann-Whitney U-test to compare the AnxA1 expression between patients and controls in renal tissues and to compare the AnxA1 expression in LN patient groups. Mann-Whitney test was also used to study the association between AnxA1 expression and qualitative clinical, serological, and histological features of lupus. While, for correlation between AnxA1 expression scores and quantitative features of the disease, we used the Spearman correlation. A p-value less than 0.05 were considered as statistically significant.

Results

Characteristics of the study subjects

A total of 24 patients, from south Tunisia with sex ratio f/M=4/1, were included in the study. The median age of patients was 34 years (13-80 years). Lupus duration at the time of the biopsy was ranged from 1 to 14 years (median =5.5 years), while it was from 1 to 9 years (median=2) for nephropathy. All patients had proteinuria, 20% had hematuria. The LN were classified according to the ISN/RPS classification; 2patients had class II, 6 class III, 4 class IV, 1 class V, 3 class III+V and 8 class IV+V. Histological and serological characteristics of patients, including immunoglobulin (Ig) deposits, different types of glomeruli infiltration and Abs detected in sera are summarized in Table 1 and Table 2.

Table 1. Histological characteristics of lupus nephritis patients (n=24)

Histological characteristics	% of presence	Valid %
IgG deposit	80.9%	88%
IgM deposit	52.3%	88%
IgA deposit	52.3%	88%
C1q	66.6%	88%
C3	61.9%	88%
Kappa deposit	76.1%	88%
Lambda deposit	71.4%	88%
Fibrinogen deposit	50%	92%
Wire loop	31.8%	92%
Cellular crescent	9%	92%
Fibrocellular crescent	4.5%	92%
Necrosis	16.6%	92%
Cell debris	50%	92%
Hyaline thrombi	9%	92%
Glomerular sclerosis	36.3%	92%
Mesangial proliferation	36.3%	92%
Synechia	9%	92%
Tubular lesion	4.5%	92%
Endocapillary proliferation	54.5%	92%
Extracapillary proliferation	54.1%	92%
Fibrocellular proliferation	9%	92%
Interstitium infiltration	54.5%	92%
Vascular lesion	4.5%	92%
Sclerosis	18.1%	92%
Tubular atrophy	13.6%	92%

Table 2. Clinical and serological characteristics of lupus nephritis patients

Clinical and Serological characteristics	Median or % of presence	Valid %
Plasma creatinine	100.5	
Proteinuria	100%	
Hematuria	20%	
Nephrotic syndrome	33%	
Activity index	6	
Sclerosis index	1	
Malar rash	47%	72%
Photosensibility	52.9%	72%
Mouth ulcers	5.8%	68%
Anemia	93.7%	64%
Arthritis	5.88%	68%
Polyarthralgia	64.7%	68%
Pleurisy	58.8%	68%
Pericarditis	11.7%	68%
Anti-DNA Abs	70.5%	68%
Anti-nucleosome Abs	76.4%	68%
Anti-Sm Abs	25%	64%
Anti-RNP Abs	35.2%	68%
Anti-SSA Abs	35.2%	68%
Anti-SSB Abs	37.5%	64%
Anti-Scl-70 Abs	18.7%	64%
Anti-PM/SCL Abs	18.7%	64%
Anti-centromere Abs	6.3%	64%
Anti-PCNA Abs	6.6%	60%
Anti-ribosomal Abs	18.7%	64%
anti-histone Abs	35.2%	68%
Hypocomplementemia CH50	30%	41%

Renal Immunostaining

Histology assessment of AnxA1 expression in renal tissues showed different scores in patient and control's biopsies. The non-parametric Mann-Whitney test showed that AnxA1 was expressed in tubules and glomeruli of both patients and controls. While, AnxA1 glomerular distribution was higher in patient's biopsies than in controls (p=0.00019), while, AnxA1 tubular distribution didn't show any difference between patients and controls (Fig.1).

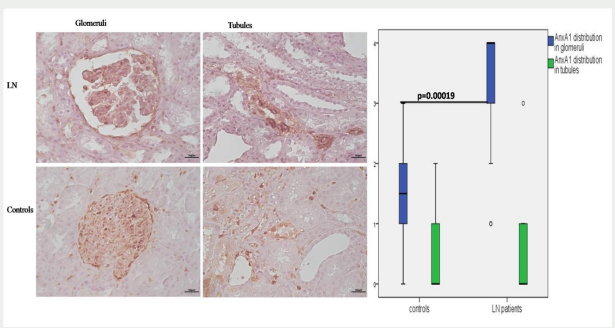

Figure 1. Immunohistochemical staining of AnnexinA1 in kidney tissues; in glomeruli and tubules of LN patient and controls
LN: Lupus nephritis

Within LN classes, AnxA1 intensity was higher in glomeruli of patients with classes III compared to patients with Class II and IV (p=0.050, p=0.023 respectively). The analysis of fibrosis and inflammatory cells infiltration scores didn't show any significant differences between LN classes.
When comparing AnxA1 expression between different LN groups, our results showed that AnxA1 intensity expression in glomeruli was significantly higher in severe proliferative group G1 than non severe proliferative group G2 (p=0.019). However, AnxA1 intensity expression in tubule was not different between the two groups (Fig.2).

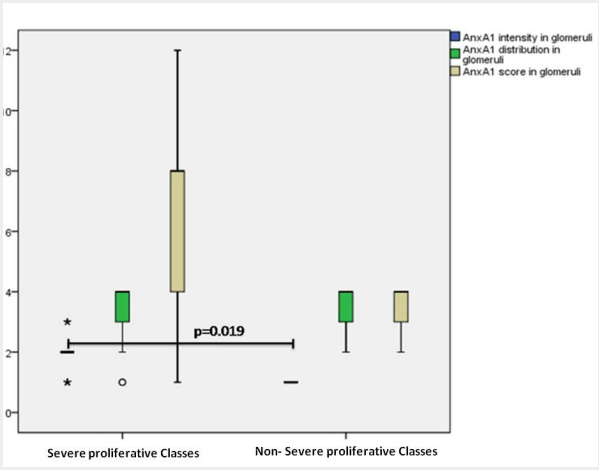

Figure 2. Annexin A1 expression in LN groups: severe proliferative classes (III, IV and III+V, IV+V), non severe proliferative classes (II, V)

Spearman correlation test showed a negative correlation between AnxA1 distribution and intensity in glomeruli with their correspondents in tubules (Table 3).
When studying correlation between AnxA1 expression in renal tissues and clinical, serological and histological presentation of patients (Table 4), we found that in tubules, AnxA1 expression was lower in patients with anti-DNA Abs, anti-nucleosome Abs and CH50 low (hypocomplementemia). Whereas, we found a positive correlation between AnxA1 expression in tubules and infiltration of interstitium by inflammatory cells.

Table 3. Spearman correlation between AnxA1 expression in tubules and AnxA1 expression in glomeruli

	AnxA1 intensity in tubules		**AnxA1 distribution in tubules**		**AnxA1 score in tubules**	
	r	p	r	p	r	p
AnxA1 intensity in glomeruli	_	NS	_	NS	_	NS
AnxA1 distribution in glomeruli	-0.319	0.070	-.483	0.004	-.473	0.005
AnxA1 score in glomeruli	-.364	0.037	-.481	0.005	-.418	0.015

Abbreviation: AnxA1, Annexin A1, NS, non significant

Table 4. Association between AnxA1 expression and serological characteristics

	AnxA1 intensity in tubules		**AnxA1 distribution in tubules**		**AnxA1 score in tubules**	
	+/-	p	+/-	p	+/-	p
Anti-DNA Ab	-	0.009	-	0.008	-	0.08
Anti- nucleosome Ab	-	0.003	-	0.004	-	0.024
Hypocomplementemia CH50		NS		NS	-	0.021

Abbreviation: AnxA1, Annexin A1, NS, non significant

Discussion

AnxA1 is an endogenously produced anti-inflammatory protein which many studies have been devoted, last years, for its contribution in the development of human diseases, like type 2-diabete [16] and pancreatic cancer [17]. Many arguments are for the implication of AnxA1 in the physiopathology of LN. Indeed, in our previous case-control study of ANXA1 polymorphisms in systemic lupus erythematosus, we found the rs3739959>G of ANXA1 gene to be associated with LN susceptibility [18]. Alice B et al had also found that high levels of anti-AnxA1 were associated with renal complications in lupus patients [19]. To investigate this hypothesis, we characterized the AnxA1 expression in LN biopsies, by conducting an immuno-staining of AnxA1 in renal tissues. Our results showed a higher expression of AnxA1 in glomeruli than in tubules of both patients and controls. This is in concordance with the HUMAN PROTEIN ATLAS site data which indicate that in healthy renal tissues, tubules weakly express the AnxA1, while glomeruli express higher levels of AnxA1, more than tubules. Besides, Shuk-Man Ka et al found that AnxA1 mRNA was weakly expressed in renal tubules of normal controls and in regenerating tubules in renal tissues of patients with different nephropathies [10].
The expression of AnxA1 was differently modulated in many diseases depending on physiopathology of the disease. In human cancers, the AnxA1 expression was different from one type to another. It was lowly expressed in prostate cancer, while, highly expressed in human breast cancer compared to controls. Xiao-Feng. B et al,

reported an overexpression of AnxA1 in pancreatic cancer and suggested the protein to be used as a biomarker for the diagnosis of this disease [17]. A recent study reported an up-regulation of AnxA1 in the sera of type 1 diabetes patients [16].

In the present study, we found a high distribution of AnxA1 in patients with different LN classes compared to controls. This could be explained by the fact that AnxA1 is released by apoptotic polymorphonuclear neutrophils and apoptotic mesangial cells during inflammatory reaction [20].

AnxA1 expression was evaluated in some glomerular disorders, including IgA nephropathy, diabetic nephropathy and LN. Patients with glomerular disorders showed high levels of AnxA1 expression in renal tissues except those with minimal change disease (MCD) and controls who expressed very little AnxA1 in their glomeruli. These findings are in concordance with our results [10].

The main conceptually new of this study is the comparison of AnxA1 expression between different classes of LN. Our results showed that patients with severe proliferative classes showed a higher expression of AnxA1 in their glomeruli compared to non severe proliferative classes. These results suggest the presence of a link between AnxA1 expression and the severity of LN, as was mentioned in previous studies. SM. Ka et al showed higher expression of AnxA1 in secondary nephropathy (diabetic nephropathy and LN) than primary proliferative nephropathy (IgA nephropathy and crescentic glomerulonephritis) in which AnxA1 expression was higher than in non-proliferative nephropathy (MCD, membranous glomerulonephritis and focal segmental glomerulosclerosis) [10].

The difference of AnxA1 expression that we found could be explained by the mechanisms of LN physiopathology. In fact, renal injury in LN may result from auto-Abs binding to circulating antigens, or auto-Abs that bind to antigens deposited from the circulation in glomerular and vessel walls, causing in situ immune complex formation. Fc receptor and complement binding, then initiate an inflammatory and cytotoxic reaction [21]. When this reaction is directed toward podocytes in the setting of membranous nephropathy, immune complex formation occurs along the subepithelial side of the glomerular basement membrane leading to membranous nephropathy corresponding to class V. Whereas, when a cytotoxic reaction is directed toward endocapillary cells, it leads to the endocapillary proliferative and exudative inflammatory reaction that follows subendothelial immune complex formation as seen in proliferative class III and IV [21].

Usually, endocapillary proliferative lesions are associated with leukocyte accumulation especially monocytes and polynuclears [22]. Since proliferative classes are characterized by polynuclear infiltration in addition to mesangial proliferation, we can suggest neutrophils, which express the higher level of AnxA1, as the source of the high intensity of AnxA1 in severe proliferative classes glomeruli compared to non severe proliferative classes.

Feng Yu et al, explained, in a review published 2017, the different types of infiltration associated with renal injury in LN. Glomerular endocapillary and mesangial proliferation as well as infiltration of inflammatory cells were described and used for the differentiation of different LN classes. Whereas in tubules, the infiltration of lymphocytes between tubular epithelial cells was described and used [23].

These two groups of immunity cells (neutrophils and lymphocytes) show different expressions of AnxA1 under the regulation of glucocorticoids. In fact, administration of glucocorticoids to healthy human volunteers leads to an increase in the levels of annexin A1 expression of circulating monocytes and neutrophils [24] and to a decrease of AnxA1 expression by T-cells [25]. Taking attention to these knowledges, we studied the correlation between corticosteroids treatment and the AnxA1 expression in LN patients. Our results showed that there is no significant correlation between AnxA1 expression in renal tissues and corticosteroids treatment, which indicates that AnxA1 expression depend on types of proliferation in renal diseases with no relation to the corticosteroids treatment. These interesting finding highlight the important role of AnxA1 expression in glomeruli in the LN physiopathology. However, no significant association was found with AnxA1 in glomeruli and clinical, serological and histological data of LN patients. On the contrary, the high AnxA1 expression in tubules was associated with anti-DNA and anti-nucleosome Abs presence and hypocomplementia CH50. In a previous study conducted in our research laboratory, both anti-nucleosome and anti-DNA Abs were suggested as useful markers of LN assessment and of disease activity [26]. Basing on these finding, we suggest AnxA1expression on tubules to be associated with the LN severity.

Evidence of activation of apoptosis has been described in experimental models and human acute kidney injury [27]. The intrinsic pathway of apoptosis is initiated by cell stress which results in the release of apoptogenic factors that interact to activate caspasa-9 while the extrinsic pathway leads to the activation of caspase-8. Caspase-9 or caspase-8 activates effector caspases like caspase-3 [28]. Once the death cell pathways are activated, apoptotic tubular cells express “eat-me” signals, such as KIM-1, to facilitate their identification by macrophages. Then, apoptotic cells are eliminated by adjacent cells before loss of cell membrane permeability [29].

According to these knowledges, we suggest AnxA1 to be expressed by tubular cells as a mechanism of resolution of inflammation. In fact, AnxA1 was demonstrated to activate cell death pathway, in inflammatory conditions, overriding the prosurvival signals that cause prolonged lifespan of neutrophils. It activates the caspase-3 cleavage, the activation of Bax and inhibits the BAD phosphorylation [30]. Scannell and his collaborators demonstrated that apoptotic neutrophils release AnxA1 to the outer plasma membrane, which acts on macrophages, promoting the efferocytosis; the elimination of apoptotic cells [20].

Conclusion

In conclusion, our finding demonstrated that AnxA1 is more expressed on renal biopsies of LN patients compared to controls. Within LN patients, our results suggest that

AnxA1 could be used to differentiate between severe proliferative and non severe proliferative classes. However, additional study is required to use this protein in the diagnosis of LN disease.

References

1. Tecklenborg J, Clayton D, Siebert S, et al. The role of the immune system in kidney disease. Clin Exp Immunol. 2018 ; 192(2):142-150.
2. Kurts C, Panzer U, Anders HJ, et al. The immune system and kidney disease: basic concepts and clinical implications. Nat Rev Immunol. 2013 Oct; 13(10):738-53.
3. Robyn C, Carolyn J. K. Immune-mediated renal disease. Immunologic disorders. 2003. DOI: http://doi.org/10.1067/mai.2003.126
4. Manole C, Inimioara M C, Isabela S, et al. Manifestations of Systemic Lupus Erythematosus. Maedica (Bucur). 2011 Oct; 6(4): 330–336.
5. Desmond Y.H. Yap, Colin S.O. Tang, Maggie K.M. Ma, et al. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrology Dialysis Transplantation. 2012
6. Kiremitci S, Ensari A. Classifying lupus nephritis: an ongoing story. ScientificWorldJournal. 2014;2014:580620. doi:10.1155/2014/580620
7. Jan J W, Vivette DD, Melvin MS et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol. 2004;15(2):241-50. Doi:10.1097/01.asn.0000108969.21691.5d.
8. Podolska MJ, Biermann MH, Maueröder C, et al. Inflammatory etiopathogenesis of systemic lupus erythematosus: an update. J Inflamm Res. 2015;8:161-171. 2015 Aug 20. doi:10.2147/JIR.S70325
9. US. Gaipl, A. Sheriff, S. Franz et al. Inefficient Clearance of Dying Cells and Autoreactivity. Curr Top Microbiol Immunol. 2006 ;305 :161-76. doi :10.10007/3-29714-6_8
10. Shuk-Man Ka, Pei-Yi T, Tai-Kuang C. Chao, et al. Urine Annexin A1 as an Index for Glomerular Injury in Patients. Dis Markers, 2014;2014:854163. Doi:10.1155/2014/854163
11. Michelle A S, Juliana PV, Mauro MT, et al. Annexin A1 and the Resolution of Inflammation: Modulation of Neutrophil Recruitment, Apoptosis, and Clearance. Journal Immunol Res. 2016;2016:8239258. Doi: 10.1155/2016/8239258.
12. Mathias U, Per O, Linn F, et al.Towards a knowledge-based Human Protein Atlas. Nature Biotechnology .2010 ; 28, 1248–1250
13. Madeeha HS, Egle S. Annexin A1: Uncovering the Many Talents of an Old Protein. Int J Mol Sci.2018; 31;19(4):1045. Doi: 10.3390/ijms19041045
14. Nesrine E, Raouia F, Lobna A, et al.The Increased Expression of Toll-Like Receptor 4 in Renal and Skin Lesions in Lupus Erythematosus. Journal of Histochemistry & Cytochemistry, 2017;1–10.
15. D.Geoffrey V, Abdelghani T, Ajeetkumar G et al. Quantitative comparison of immunohistochemical staining intensity in tissues fixed in formalin and Histochoice. Anal Cell Pathol.1997; 15(2):119-29
16. Gareth SD. P, Massimo C, Rodrigo A L, et al. Identification of AnnexinA1 as an Endogenous Regulator of RhoA, and Its Role in the Pathophysiology and Experimental Therapy of Type-2 Diabetes. Front Immunol. 2019; 27;10:571. Doi: 10.3389/fimmu.2019.00571
17. Xiao-Feng B, Xiao-Guang N, Ping Z, et al. Overexpression of annexin 1 in pancreatic cancer and its clinical significance. World J Gastroenterol: 2004;15;10(10):1466-70.doi: 10.3748/wjg.v10.i10.1466
18. Fatma D, Hend H, Olfa A, et al. Annexin A1 and its receptor gene polymorphisms in systemic lupus erythematosus in the Tunisian population. Clinical Rheumatology. 2022. Doi: 10.1007/s10067-022-06057-7
19. Alice B, Augusto V, Maurizio B, et al. Multi-antibody composition in Lupus nephritis: Isotype and antigen specificity make the difference. Autoimmun Rev. 2015; 14(8):692-702. Doi:10.1016/j-autrev:2015.04.004
20. Michael S, Michelle B F, Andreas Stefani, et al. Annexin-1 and Peptide Derivatives Are Released by Apoptotic Cells and Stimulate Phagocytosis of Apoptotic Neutrophils by Macrophages. Immunol. 2007;178 (7) 4595-4605.
21. Nowling TK, Gilkeson GS. Mechanisms of tissue injury in lupus nephritis. Arthritis Res Ther. 2011;13(6):250. doi:10.1186/ar3528
22. Barrera García A, Gómez-Puerta JA, Arias LF, et al. Infiltrating CD16+ Are Associated with a Reduction in Peripheral CD14+CD16++ Monocytes and Severe Forms of Lupus Nephritis. Autoimmune Dis. 2016;2016:9324315. doi:10.1155/2016/9324315
23. Feng Y, Mark H, Richard G, et al. Redefining lupus nephritis: Clinical implications of pathophysiologic subtypes. Nat Rev Nephrol. 2017;13(8):483-495.
24. Goulding NJ, Godolphin JL, Sharland PR, et al. Anti inflammatory lipocortin 1 production by peripheral blood leucocytes in response to hydrocortisone. Lancet,16;335(8703):1416-8, 1990.
25. Mauro P, Fulvio D. Annexin A1 and glucocorticoids as effectors of the resolution of inflammation. Nat Rev Immunol, 9(1):62-70, 2009.
26. Haddouk S, Hachicha H, Marzouk S, et al. Anti-nucleosome antibodies may predict lupus nephritis and severity of disease in systemic lupus erythematosus.Indian Journal of Rheumatology. 2010; 165-170.
27. Diego M S, Jonay P, Miguel F B, et al.Targeting of regulated necrosis in kidney diseaseAnálisis dirigido de la necrosis regulada en la enfermedad renal. Nefrologia. 2018; 125-135.
28. Ana BS, Beatriz S, Marta R, et al. Mechanisms of Renal Apoptosis in Health and Disease. J Am Soc Nephrol. 2008; 19(9):1634-42.
29. Esmeralda C R, Raul F P, Catalina MC, et al. Kidney Injury Marker 1 and Neutrophil Gelatinase-Associated Lipocalin in Chronic Kidney Disease. Nephron. 2017;136:263-267.
30. Vago J. P., Nogueira C. R., Tavares L. P., et al. Annexin A1 modulates natural and glucocorticoid-induced resolution of inflammation by enhancing neutrophil apoptosis. Journal of Leukocyte Biology. 2012;92(2):249–258. doi: 10.1189/jlb.0112008.