Journal of Clinical Nephrology & Kidney Diseases

Short Communication
Published: 18 Feb, 2020

A Novel Concept May Explain How Immune Complexes Interact with Highly Cationic Histones Released by Activated Neutrophils Nets Act in Synergy with the Plethora of Neutrophils Pro-Inflammatory Agonists Leading to the Development of Autoimmune Nephritis -A Working Hypothesis

Ginsburg I[1], Koren E[2] and Ido Ben Dov[3]*

[1]*Department of Dentistry, The Hebrew University, Israel*

[2]*Department of Research and Development, Koren E Clexio Biosciences Ltd, Israel*

[3]*Department of Nephrology, Hadassah Hospital, Israel*

Abstract

Recent studies have pointed out that highly cationic histones released by PMNs netosis may be major agents in autoimmune lupus since they have high affinity to various kidney sites and can be expected to play a key role in autoimmune glomerular disease.

Similarly to antibodies, cationic peptides such a nuclear histone can also act as potent opsonic agents capable of binding by strong electrostatic forces to negatively charged domains in immune complexes and in complement components resulting in their endocytosis and deposition in various parts of the kidney. It is also proposed that to prevent such events, highly anionic heparin and heparinoids, may be effective drugs since these may effectively neutralize histones activities but provided that agents such as steroids, methotrexate and colchicine, all potent inhibitors of neutrophils functions, and antibodies to TH1 cytokines be essential to treat nephritis and to prevent kidney failure. However, the main cause of kidney damage is eventually caused by the plethora of toxic pro inflammatory agents delivered by activated neutrophils and macrophages.

OPEN ACCESS

Correspondence:
Ginsburg I, Department of Dentistry, The Hebrew University, Jerusalem, Israel,
E-mail: ahendler@012.net.il

Received Date: *16 Jan 2020*
Accepted Date: *12 Feb 2020*
Published Date: *18 Feb 2020*

Citation:
Ginsburg I, Koren E, Dov IB. A Novel Concept May Explain How Immune Complexes Interact with Highly Cationic Histones Released by Activated Neutrophils Nets Act in Synergy with the Plethora of Neutrophils Pro-Inflammatory Agonists Leading to the Development of Autoimmune Nephritis –A Working Hypothesis. J Clin Nephrol Kidney Dis. 2020; 5(1): 1025.

Introduction

In autoimmune lupus nephritis, activated neutrophils (PMNs) their released nets ('netosis') rich in a nucleosome and in highly cationic histones and in additional polycations, have been proposed to be involved as major key agents in the pathogenesis of lupus nephritis [1-4]. We here by propose a novel hypothesis to explain the mechanisms and pathogenicity of autoimmune nephritis. Localization in the kidneys of immune complexes and complement components from the circulation are seen mainly in the sub endothelial, mesangial, and subepithelial areas [3]. It is hereby suggested, that highly cationic agents such as histones [5], LL37, defensins and elastase released by activated PMNs nets (traps) [5-7], can act not only as bactericidal and cytocidal agents but, may also function as potent opsonins (opsonic agents) with properties similar to antibodies [8]. The polycationic opsonins can now bind by strong electrostatic forces to negatively-charged domains in immune complexes and in complement components facilitating their deposition (endocytosis) not only in subendothelial mesangial, and subepithelial areas of the kidney but paradoxically, can also induce their endocytosis by kidney cells [8-10] (see below) eventually causing renal damage and finally also renal failure. These novel suggestions originated from our previous observations showing that hemolytic streptococci, *Candida albicans* and even whole cell nuclei pre-coated by cationic polypeptides such as histones, could effectively bind to and also undergo endocytosis not only by professional phagocytes such as PMNs and macrophages but, also by endothelial cells, fibroblast and even by epithelial cells [8-10], However, as already proposed in many of our earlier publications, these were damage to mammalian cells seen in various inflammatory, infectious, in post infectious sequelae but, most probably also in autoimmune disorders, may be initiated by

a tights energy among the plethora of proinflammatory agonists released from activated PMNs and macrophages [11-14]. These agents include: histones, LL37, defensins, proteinases, reactive oxygen and nitrogen species, PLA2, lysophosphatides, fatty acids and many hydrolases [11-14]. Also, Th1cytokines generated can stimulate the recruitment, migration and localization in the kidney of additional PMNs which upon activation in the inflamed cites may further create waves of toxic pro inflammatory vicious toxic cycles [15,16]. To abolish or mitigate the toxic actions of the cationic opsonins, it maybe be advised that highly anionic heparin [17] be administered to patients as this may suppress tissue damage by its ability to strongly neutralize the synergistic toxic action induced by polycations. Also, heparin and heparinoids were shown to prevent the binding of immune complexes containing nucleosomal antigens to the glomerular basement membrane and thus delayed the onset nephritis [18]. An attention has also been focused on the role of electrostatic charges in the pathogenesis of immune complex-mediated tissue injury [19]. These authors have examined the ability of cationic histone and of the histone mimic poly L-arginine to modulate acute immune complex-mediated tissue injury. However, we propose that this is provided that in addition to anionic heparins [17-20] combinations among corticosteroids, methotrexate, colchicine and cyclophosphamide [21], but, also with additional suppressors of the PMNs functions chemotaxis and phagocytosis, and also anti TNF alpha [21], are administered to lupus nephritis patients.

It might be also be important, at this point, to note that the mechanisms of tissue damage in inflammation and in post inflammatory episodes induced by activated PMNs [11-14] and also in autoimmune episodes is highly similar to those seen in infections caused by group-A hemolytic streptococci [22]. In both cases, a typical synergy among secreted agonists is responsible for cell and tissue damage [12,22-23].

Conclusion

Several overlapping and also succession steps may help to explain the development of autoimmune nephritis.

1. Generation of autoimmune complexes and activation of the complement cascades [2,3].

2. The release from PMNs nets (netosis) of highly cationic toxic histones and formation of citrullinated histones [5-7].

3. Cationic Histone may also function as potent opsonic agents possessing properties similar to antibodies [8].

4. Opsonic histones, can function as opsonins and may interact with and also bind by strong electrostatic forces to negatively-charged domains on immune complexes and complement components, facilitating their binding, deposition and possibly also their internalization by kidney cells.

5. PMNs and Macrophages migrating to the kidney undergo activation to' release into the surrounding media a plethora of toxic pro inflammatory agonists. These mainly include: cationic peptides, oxidants, proteinases, membrane -perforators phospholipases, fatty acids which may all act synergistically to injure heart valves, myocardial cells, joint synovial and also cartilage [11-15].

6. Protection against the progressing tissue damage in nephritis might be provided by highly anionic heparin and heparinoids [18-20] which can neutralize the toxicity of polycations. This is provided that these are also combined with drugs such as, steroids, methotrexate and colchicine and novel drugs [21]. All these potent anti-inflammatory agents may suppress chemotaxis, phagocytosis and alsoTh1 cytokines can be inhibited by drugs which affect leukocytes recruitment [21] heparins to suppress histones and also role in cell death [23].

7. Toxic oxidants and proteinases released by PMNs and macrophages may be controlled to some extent by multi drug strategies [23] and by the low molecular weight anti- oxidants: glutathione, ascorbate, N- acetyl cysteine as well as by certain plant polyphenols, and also by the anti proteinase, aprotinin and also by additional multidrug strategies [23].

8. Can we learn from the pathogenesis of group A hemolytic streptococcal infections how tissues are injured in post inflammatory sequelae [22].

Taken together, we may now conclude that similar mechanisms of tissue damage may also occur in rheumatoid arthritis, ulcerative colitis Crohn's disease and perhaps also in additional autoimmune disorders.

References

1. Kaplan MJ. Role of neutrophils in systemic autoimmune diseases. Arthritis Res Ther. 2013;15:219.
2. Cecchi I, Arias de la Rosa I, Menegatti E, Roccatello D, Collantes-Estevez E, Lopez-Pedrera C, et al. Neutrophils: Novel key players in Rheumatoid Arthritis. Current and future therapeutic targets. Autoimmun Rev. 2018;17(11):1138-49.
3. Mannik M. Deposition of circulating immune complexes in glomeruli. Chronic Renal Disease. Transplant. 1985;29-38.
4. Vogt A, Schmiedeke T, Stöckl F, Sugisaki Y, Mertz A, Batsford S. The role of cationic proteins in the pathogenesis of immune complex glomerulonephritis. Nephrol Dial Transplant. 1990;5(Suppl 1):6-9.
5. Kaplan MJ, Radic M. Neutrophil extracellular traps (NETs): Double-edged swords of innate immunity. J Immunol. 2012;189(6):2689-95.
6. Yang H, Biermann MH, Brauner JM, Liu Y, Zhao Y, Herrmann M. New Insights in to Neutrophil Extracellular Traps: Mechanisms of Formation and Role in Inflammation. Front Immunol. 2016;7:302.
7. Brinkmann V, Zychlinsky A. Beneficial suicide: Why neutrophils die to make NETs. Nat Rev Microbiol. 2007;5(8):577-82.
8. Ginsburg I. Cationic polyelectrolytes: A new look at their possible roles as opsonins, as stimulators of respiratory burst in leukocytes, in bacteriolysis, and as modulators of immune-complex diseases (A review hypothesis). Inflammation. 1987;11(4):489-515.
9. Ginsburg I, Sela MN, Morag A, Ravid Z, Duchan Z, Ferne M, et al. Role of leukocyte factors and cationic polyelectrolytes in phagocytosis of group A streptococci and *Candida albicans* by neutrophils, macrophages, fibroblasts and epithelial cells: modulation by anionic polyelectrolytes in relation to pathogenesis of chronic inflammation. Inflammation. 1981;5(4):289-312.
10. Hubner GE, Voigt W-H, Schlumberger HD, Ginsburg I. Poly-L-arginine 'opsonizes' nuclei for phagocytosis by mouse fibroblasts. IRCS Medical Science. 1985;13(10):934-5.
11. Varani J, Ginsburg I, Schuger L, Gibbs DF, Bromberg J, Johnson KJ, et al. Endothelial cell killing by neutrophils. Synergistic interaction of oxygen products and proteases. Am J Pathol. 1989;135(3):435-8.
12. Ginsburg I. Could synergistic interactions among reactive oxygen species, proteinases, membrane-perforating enzymes, hydrolases, microbial hemolysins and cytokines be the main cause of tissue damage in infectious and inflammatory conditions? Med Hypotheses. 1998;51(4):337-46.

13. Ginsburg I, Kohen R. Cell damage in inflammatory and infectious sites might involve a coordinated ''cross-talk'' among oxidants, microbial hemolysins and amphiphiles, cationic proteins, phospholipases, fatty acids, proteinases and cytokines (An Overview). Free Radic Res. 1995;22(6);489-517.

14. Ginsburg I, Kohen R. Synergistic effects among oxidants, membrane-damaging agents, fatty acids, proteinases, and xenobiotics: killing of epithelial cells and release of arachidonic acid. Inflammation. 1995;19(1):101-8.

15. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol. 2013;13(3):159-75.

16. Chen DY, Chen YM, Wen MC, Hsieh TY, Hung WT, Lan JL. The potential role of Th17 cells and Th17-related cytokines in the pathogenesis of lupus nephritis. Lupus. 2012;21(13):1385-96.

17. Wildhagen KC, Garcíade Frutos P, Reutelings perger CP, Schrijver R, Aresté C, Ortega-Gómez A, et al. Nonanticoagulant heparin prevents histone-mediated cytotoxicity *in vitro* and improves survival in sepsis. Blood. 2014;123(7):1098-101.

18. Van Bruggen MC, Walgreen B, Rijke TP, Corsius MJ, Assmann KJ, Smeenk RJ, et al. Heparin and heparinoids prevent the binding of immune complexes containing nucleosomal antigens to the GBM and delay nephritis in MRL/lprmice. Kidney Int. 1996;50(5):1555-64.

19. Warren JS, Ward PA, Johnson KJ, Ginsburg I. Modulation of acute immune complex-mediated tissue injury by the presence of polyionic substances. Am J Pathol. 1987;128(1):67-77.

20. Xu J, Zhang X, Pelayo R, Monestier M, Ammollo CT, Semeraro F, et al. Extracellular histones are major mediators of death in sepsis. Nat Med. 2009;15(11):1318-21.

21. Li P, Zheng Y, Chen X. Drugs for Autoimmune Inflammatory Diseases: From Small Molecule Compounds to Anti-TNF Biologics. Front Pharmacol. 2017;8:460.

22. Ginsburg I, Ward PA, Varani J. Can we learn from the pathogenetic strategies of group A hemolytic streptococci how tissues are injured and organs fail in post-infectious and inflammatory sequelae? FEMS Immunol Med Microbiol. 1999:25(4):325-38.

23. Chen R, Kang R, Fan XG, Tang D. Release and activity of histone in diseases. Cell Death Dis. 2014;5(8):e1370.