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Short Communication

A Novel Approach That May Explain the Role of *Staphylococcus aureus*, Polycations, Neutrophils Pro-Inflammatory Agonists and the Bacteriolysis and Auto Immune Phenomena as Possible Major Events in the Pathogenesis of Atopic Dermatitis: A Working Hypothesis

Isaac Ginsburg[1*], Erez Koren[2]

[1]Faculty of Dental Medicine, Institute for Dental Research, The Hebew University, Jerusalem, Israel; [2]Department of Dental research, Clexio Biosciences LTD, Raanana, Israel

INTRODUCTION

The aim of the present short communication is to shed a novel light on the auto immune disorder atopic dermatitis by discussing the possible role played by the plethora of toxic agents released by *Staphylococcus aureus* which can act in a tight synergism with neutrophils derived cationic polyelectrolytes as related to the pathogenesis of atopic dermatitis (AD) [1,2]. This disorder results in inflammation of the skin characterized by itchiness, red skin, a rash, by the accumulations of large numbers of *Staphylococcus aureus* their toxins [2] and pro-inflammatory agents secreted by migrating neutrophiles [3], are considered the main cause of AD pathogenicity.

ABOUT THE STUDY

Patients with AD, exhibit defects in innate and acquired immune responses which result in a heightened susceptibility to bacterial, fungal and viral infections but most notably associated with colonization by S. *aureus*. Several toxins produced by this microorganism [2] may exacerbate disease activity by the induction of specific IgE and the activation of various cell types including Th-2 cells, eosinophils and keratinocytes.

The idea that a mechanism of autoimmunity could play a role in the pathogenesis of atopic dermatitis is based on the observation that patients with atopic dermatitis display IgE reactivity to a variety of human protein antigens. A broad spectrum of at least 140 IgE-binding self-antigens associated with atopic dermatitis has been demonstrated which might promote, and perpetuate, skin inflammation by binding IgE antibodies or activating specific T cells [4]. Even if the presence of autoreactivity seems to be associated with the severity of the disease, the role of auto autoimmunity in atopic dermatitis is still not clear.

In the present communication, we offer a novel approach that may shed a new light on the mechanisms of AD pathogenicity. We suggest that during inflammation in the skin caused by staphylococci, migrating neutrophils which accumulate in large numbers can undergo netosis [5,6].

This is a phenomenon where long threads (Nets) rich in a nucleosome and in cationic histone and also in various other highly toxic cationic peptides are formed. Such poly cations can function not only as bactericidal and cytocidal agents but, also as potent opsonic agents [7] possessing properties similar to antibodies. Thus, by binding by strong electrostatic forces to negatively-charged domains in immune complexes, complement components and also upon staphylococcal cells, these highly-charge cationic polyelectrolytes may facilitate the deposition and internalization of immune complexes and staphylococci not only by professional phagocytes such as neutrophils and macrophages but, also by endothelial cell, adipocytes keratinocytes, and also by epithelial cells [8,9].

Intra cellularly, staphylococci may now be protected and can survive unharmed until the immune system of the host is lowered and can then have a chance for are attack employing their rich arsenal of pro-inflammatory agents [1,2] causing injury to skin cells.

Eventually, however, the major damage induced to skin cells, may be due to migrating PMNs and their released toxic agents. Upon *in situ* activation, PMNs can shed out into the surrounding media a plethora of pro-inflammatory agents [10-13]. These include: reactive oxygen and nitrogen species, HOCl, cationic histone, cationic elastase, other poteinases, defensins, LL37, cathelicidines, phospholipase A2, and lysophosphatides.

However, these agents can now also be available to further act in a synergistic manner with the plethora of pro-inflammatory agonist released by staphylococci to cause injury to skin cells [2]. The staphylococcal agents released include: α, β, γ and δ hemolysins (leukocidins), toxic shock syndrome toxin, Panton-

Correspondence to: Isaac Ginsburg, Faculty of Dental Medicine, Institute for Dental Research, Ein Kerem Campus, The Hebew University, Jerusalem, Israel, E-mail: ginsburg@mail.huji.ac.il

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Valentine leukocidin, a phospholipase, coagulase and deoxyribonuclease, and staphylokinase.

However, damage to skin in AD may also be significantly aggravated by the phenomenon of bacterioysis [14].

This is a process where cationic peptides such as histones, cationic lysozyme and certain antibiotics [15] may activate the autolytic wall enzymes of *staphylococcus aureus* to release into the surrounding media toxic cell wall components such as lipoteichoic acid peptidoglycan and endotoxins [14]. Non biodegraable cell wall components of bacteria may also persist for a long time within macrophage to further cause chronic damage to skin [16,17].

Intra cellularly, viable staphylococci may be now protected and can survive unharmed until the immune system the host is lowered and can now have a chance for a re attack employing their rich arsenal of pro-inflammatory agents [2] to injure the skin cells [18-24].

To ameliorate and perhaps also prevent skin damage as seen in staphylococcal-induced AD, it might be suggested to administer highly anionic heparin and heparinoids which may be able to effectively neutralize polycations [25]. However, this is provided that multi drug strategies [26] including agents such as corticosteroids, methotrexate, colchicine, cyclophosphamide and additional suppressors of the PMNs functions chemotaxis and phagocytosis and also antibiotics such as vancomycine, be also used.

Recent reports approved new, injectable biologic monoclonal antibody called dupilumab (Dupixent) which is used to treat people with severe disease who do not respond well to other treatment options [27,28].These newer medication, don't have a long track record in terms of how well it helps people. Also, creams containing drugs called calcineurin inhibitors such as tacrolimus (Protopic) and pimecrolimus (Elidel) affect the immune system. They are used by people older than age 2 to help control the skin reaction.

CONCLUSION

The present short presentation suggests a novel approach which may shed a new light on how staphylococci and their secreted pro-inflammatory agent [2] and immune complexes can act in concert with polycations, and with exo products released from activated PMNs [10-13] to injure skin as seen in AD. Internalized staphylococci [18-24] may persist intra cellularly, unharmed, and capable of re-emerging from cells to re attack skin. Treatment of Atopic Dermatitis with Biologic Drugs my better ameliorate the viscous toxic cycles [27,28].

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