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Research Article: The role of neutrophils and by macrophages in the pathogenesis of inflammatory and post inflammatory episodes : Major tissue damage may be inflicted by a synergy among their toxic pro inflammatory agents

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Introduction

In his manuscript we summarize the role played by the variety of pro inflammatory agents generated by neutrophils and by macrophages and how these cells may act in synergy to injure human and tissues in various inflammatory and in post inflammatory conditions .

Screening the vast published literature, we found that most of papers published on inflammation, tend to stress only the role played by a very few pro inflammatory agents as key agents in inflammation. This is unreasonable to try to understand how leukocytes kill microbial cells and injure mammalian cells in various medical conditions. This is since the PMNs and macrophages produce numerous inflammatory agents.¹⁻¹⁵

The role of neutrophils in cell damage in inflammation

Upon activation, both neutrophils and macrophages were shown to deliver long nets (traps) rich in a nucleosome and in a series of highly cationic polyelectrolytes. These include mainly: Histone, LL37, defensins, elastase, catelicidin. These cationic agents are mainly directed to kill microorganisms^{16,17} and also aid in their disintegration bacteriolysis – see below¹⁸⁻²⁰

To better understand the role of neutrophils in cell damage, we may first study the histology and images of inflamed tissues analysing for the enzyme myeloperoxidase which is a typical marker of neutrophils.²¹⁻²³

Not having a single toxic identified virulent agent such as seen in tetanus and diphtheria, which may explain the toxic effects in infections and in inflammatory and post inflammatory episodes, we need to test combinations and permutations among a large variety of key agents and to determine those minimal combinations required to injure, kill and also to disintegrate microorganisms by the bacteriolysis system.

To appreciate the richness of agents produced by neutrophils we hereby offer the reader a cumulative list of pro inflammatory agents generated neutrophils, many of which, may act in synergy to injure cells in microbial infections and in post inflammatory sequelae. May be the slogan : “ If you cannot beat them alone, join them ”. is very appropriate when dealing with multifactorial agents .

A List of Agents produced by activated neutrophils

Myeloperoxidase : An excellent marker used if one analyzes histology of organs affected by inflammation rich in neutrophils :

beta-glucuronidase, N-acetyl-beta- glucosaminidase, alpha-mannosidase, and acid phosphatase, Acid glycosidases, Plasminogen activator, Collagenase, Elastase, Lysozyme, cartilage mucopolysaccharide-degrading neutral protease from human leukocytes, Oxidants, nitrogen species nitric acid, Superoxide, Hydrogen peroxide, Gelatinase, PLA2 and arachidonic acid release, Lysophosphatides, Metalloproteinase, HOCl, (TNF), IL-1, IL-6, IL-8, and IL-12

Oncostatin M, transforming growth factor, TNF, tumor necrosis factor, interferon, LL37, interleukin-, IL-1ra, IL-1 receptor antagonist leukemia inhibitory factor, MCP-1, monocyte, chemoattractant protein-1, MIF, macrophage migration inhibitory factor

Macrophage / granulocyte- colony stimulating factor
Macrophage inflammatory protein, oncostatin M, transforming growth factor, tumor necrosis factor

A large group cytokines are involved in chemotaxis. Some cytokines can upregulate the production of other cytokines by macrophages (IL-3, GM-CSF, IFN γ) while others can inhibit it (IL-4, IL-10, IL-13, TGF β). , IL-1, IL-1ra, IL-6, IL-8, IL-10, IL-12, TNF α , IFN α , IFN γ , MCP-1, MCP-3, MIF, M-CSF, G-CSF, GM-CSF, MIP-1, MIP-2, LIF, OSM, TGF β).

The role of bacteriolysis in cell damage seen in inflammation
Inflammatory episodes, may be associated with microbial infections in addition to their exo toxins and endotoxins. Exo toxins bacteria may also undergo bacteriolysis^{24,45} due to the activation by cationic lysozyme²⁶ or by other poly cations. This is due to the activation of endogenous autolytic wall enzyme (muramidase releasing non biodegradable cell wall components such as lipoteichoic acid²⁷ and peptidoglycan^{24,25}. Such cell fragments may be stored by macrophages causing relapsing chronic arthritis²⁸⁻³⁰. This may be demonstrated by measuring muramic acid a part of the cell wall.³¹

The role played by reactive oxygen species and proteinases in cell damage

Activated neutrophils, can induce the activation of NADPH oxidase generating superoxide HOCl and additional on reactive oxygen species highly toxic to cells³².

Neutrophils also release phospholipase A_s and lysophosphatides, agents capable of puncturing holes in cell membranes^{33,34}. Neutrophils and macrophages also elaborate proteolytic enzymes^{6,9,10,11,12,35} which can act in concert with oxidants to kill cells³². It was also suggested that oxidized proteins are rapidly degraded by proteinases³².

Can anionic heparin ameliorate cell damage in inflammation?

In a very recent study¹⁵, we have suggested that the penetration of the corona virus into lung cells could be inhibited by the administration of anionic heparin.³⁶ This anionic drug can neutralize those poly cations generated by netosis^{16,17} and responsible for the uptake of the negatively charged lung cells. We suggested to treat corona patients heparin post inflammatory processes³⁶⁻³⁹

The effects of Traditional herbal preparation Padma Hepaten on inflammation

Tibetan medicine very famous for treatment of various human inflammatory disorders (see the huge literature covered by Google)⁴⁰⁻⁴²

Drugs suggested to counteract agents secreted by activated neutrophils and macrophages

These were summarized in a publication from 1999⁴³. However every agent which can retard migration of neutrophils⁴⁴ and inhibit tissue damage can be used clinically.

These include: steroids, cyclosporine, Cyclosporine, Methotrexate, Imuran (azathioprine) Plaquenil (hydroxychloroquine), CellCept (mycophenolic acid) Cytoxan, Neosar (cyclophosphamide) and agents other agents which retard chemotaxis by the cytokines storms⁴⁴

Macrophages in Inflammation and Tissue Damage

The past several years have seen evidences demonstrating that

tissue injury induced by diverse toxicants is due not only to their direct effects on target tissues but also indirectly to the actions of resident and infiltrating macrophages. Similarly to neutrophils, macrophage can also have the capacity to extend long nets rich in cationic peptides^{17,18}. Macrophages can also extend an array of mediators with cytotoxic, pro- and anti-inflammatory properties which can function to fight infections, limit tissue injury and promote wound healing. (see below a cumulative list of agents derived from Macrophages).⁴⁵

Like neutrophils, the main function of macrophages is to endocytose foreign agents that enter the body. These include microbes and other particulate matter. In addition, they eliminate apoptotic cells and recycle nutrients by digesting waste products from tissues. Macrophages are hence essential not only for immunity, but also for development and tissue homeostasis.

Understanding the precise roles of these different macrophage populations in the pathogenic response to toxicants is key to designing effective treatments for minimizing tissue damage and chronic disease and for facilitating wound repair.

Macrophages have the ability to store large amounts of undegraded agents obtained following bacteriolysis occurring following bacteriolysis and to cause a perpetuating chronic arthritis²⁴⁻³¹

The activity of macrophages can be increased by cytokines secreted by helper T cells, with interferon gamma (IFN- γ) being one of the most potent macrophage activators. In addition, these multifaceted cells are also capable of chemotaxis, namely the process of being attracted and displaced to a particular location by specific molecules⁴⁴

A list of Agents released by Macrophages :

Beta-glucuronidase, N-acetyl-beta-glucosaminidase, alpha-mannosidase,
a acid phosphatase.
Acid glycosidases
Plasminogen activator
Collagenase Cationic
Elastase Cationic
Lysozyme cationic
LL37 cationic
Defensin Cationic
Catelecidin Cationic
Gelatinase, ...Cationic
Myeloperoxidase Cationic
Defensins Cationic
Bactericidal permeability increasing agent Cationic
Cartilage muco polysaccharide-degrading neutral protease
Superoxide
Nitrogen species, nitric acid, peroxynitrate
Hydrogen peroxide
PLA2 and arachidonic acid release
Lysophosphatides
Metallo proteinases
HOCl
Macrophage / granulocyte- colony stimulating factor
Macrophage inflammatory protein
Oncostatin M
Transforming growth factor
Tumor necrosis factor
Interferon
Interleukin-
Receptor antagonist
Leukemia inhibitory factor
Monocyte chemo attractant protein-

Macrophage / granulocyte- colony stimulating factor

Macrophage inflammatory protein

Oncostatin M

Transforming growth factor

(TNF), IL-1, IL-6, IL-8, and IL-12

IL-1, IL-1ra, IL-6, IL-8, IL-10, IL-12, TNF α , IFN α , IFN γ , MCP-1, MCP-3, MIF, M-CSF, G-CSF, GM-CSF, MIP-1, MIP-2, LIF, OSM, TGF β).

Some cytokines can also regulate the production of other cytokines by macrophages (IL-3, GM-CSF, IFN γ) while others can inhibit it (IL-4, IL-10, IL-13, TGF β).

Aftermath and Conclusions

Taken together, it is suggested that pro inflammatory toxic agents released by PMNs and by macrophages can act in concert with agents released by dead cells to markedly enhance tissue as seen in severe inflammation. In addition, agents released from bacteria following bacteriolysis induced by cationic peptides and by antibiotics can be stored for long periods in macrophages to perpetuate chronic arthritis. Various agents released by dead cells include: toxic nuclear cationic enzymes “danger signals” that alert the host to cell death. Several of these molecules can be recognized by cell receptors that can stimulate the generation of pro inflammatory mediators. Additional molecules released by dead cells, can stimulate the generation of mediators also from extracellular sources. The mediators then orchestrate the inflammatory response, causing generation of various vascular and cellular components. Dead cells also release danger signals that activate dendritic cells and promote the generation of immune responses to antigens in and around the dying cells. The synergism concept of cell damage demands the collaboration among various groups of major agents such as: oxidants, HOCl, hydroxyl radical, cationic histones delivered by netosis, reactive nitrogen species such as peroxynitrate and membrane puncturing lysophosphatide. In many cases anionic heparins may block the toxicity of cationic agents released from PMN and macrophage nets. Heparin may also block endocytosis of corona and hepatitis c viruses by human tissues.

Cationic agents can also opsonize immune complexes bacteria, fungal cells for endocytosis by various body cells as seen in many autoimmune disorders. Recruitment of leukocytes to inflamed sites is controlled by various cytokine storms. Tables A and B summarize a list of agents generated by PMNs and by Macrophages.

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