ejpmr, 2021,8(11), 654-662

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

THE CLINICAL CORRELATION OF PRO-INFLAMMATORY AND ANTI-INFLAMMATORY BIOMARKERS WITH TISSUE REGENERATION: A META-ANALYSIS

Amit Gupta*[1], Himanshi Verma[1], Deepak Chandra Joshi[1], Pranav Sharma[1], Pankaj Yadav[1], Veeresh Kumar Rathour[2] and Chandra Pratap Singh[2]

[1]Department of Pharmacy, Invertis University, Bareilly, Uttar Pradesh.
[2]Department of Pharmacy, MJP Rohilkhnad University, Bareilly, Uttar Pradesh.

***Corresponding Author: Amit Gupta**

Department of Pharmacy, Invertis University, Bareilly, Uttar Pradesh.

Article Received on 21/09/2021 **Article Revised on 11/10/2021** **Article Accepted on 31/10/2021**

ABSTRACT

To monitor inflammation in a useful way, the markers utilized must be valid: they must reflect the inflammatory process under inquiry and they must be predictive of future health state. In 2019 the Nutrition and Immunity Task Force of the International Life Sciences Institute, European Branch, organized an expert group to attempt to identify robust and predictive markers, or patterns or clusters of markers, which can be used to assess inflammation in human nutrition studies in the general population. Inflammation is a normal process and there are a number of cells and mediators involved. These markers are involved in, or are formed as a result of, the inflammatory process irrespective of its cause and its location and are common to all inflammatory conditions. Currently, there is no consensus as to which indicators of inflammation best identify low-grade inflammation or differentiate between acute and chronic inflammation or between the numerous phases of inflammatory reactions. There are a variety of modifying factors that vary the concentration of an inflammatory marker at a given period, including age, diet and body fatness, among others. Measuring the concentration of inflammatory markers in the bloodstream under basal conditions is probably less informative compared with data relating to the concentration change in response to a challenge.

KEYWORDS: Inflammatory, AD progression, phagocytosis, adipocyte.

INTRODUCTION

The inflammatory response must be strictly managed to ensure efficient immune protection. It is a dynamic network that is continuously reconstructing during each person's life as a result of the interaction between our genes, lifestyles, and environments. Infections and tissue damage from the external environment and our unique internal response to stress might act as triggers to activate the inflammatory defensive response. While inflammation is part of the natural repair response for healing, and necessary in keeping us safe from bacterial and viral infections and noxious environ- mental agents, not all inflammation is beneficial. When inflammation grows persistent and persists, it can become detrimental and destructive. It is vital that inflammation is customized to the initiating stress and resolves in a timely and controlled way, to avoid disease associated with chronicity.

The cytokine network is a very complex system of immunological molecular messengers, with several levels of activation and regulation mediated through soluble receptors, receptor antago- nists, various serum mediators, as well as gene polymorphisms. Proteomic methods measuring cytokine production and expression have demonstrated further layers of complexity and control in cytokine production and expression involving long coding RNAs, siRNAs, and miRNAs, which make for challeng- ing interpretation of cytokine production and control in the inflammatory process. Many cytokines are able to function in more than one-way or ironically at various times and many act in feedback loops with the ability to auto-control their own production. Cytokine expression is also controlled by local cellular microenvironments, showing that various mechanisms exist to accomplish homeostatic immunologic regulation and effective- ness, or to conversely increase chronic immunological activation. However, what seems evident is that mirroring other physiological systems, the homeostatic regulation, titration, and modulation of immune responsiveness becomes more frail and less tightly focused with increasing age. This loosening of the cytokine balance between the pro-inflammatory and anti-inflammatory regulation or resolution mechanisms, or inflamm-aging, is a defining hallmark of both aging and age-related disorders. Recently, a wealth of research

relating the pro-inflammatory cytokines [such as IL-1, IL-6, and tumor necrosis factor-α (TNF-α)] generated from microglia has garnered great attention for its role in AD. As the most abundant immune cells in the central nervous system (CNS), microglia has long been a hotspot in AD due to their significant responses to the pathophysiology of the illness. Microglia activation have multiple impacts on AD progression: one side, activation of microglia leads to lowering Aβ buildup by boosting its phagocytosis, clearance and destruction, which reduces the formation of amyloid plaques in the brain. On the other side, chronic microglia activation leads to the release of pro-inflammatory cytokines, which initiates a pro-inflammatory cascade and subsequently contributes to neuronal damage and losses In this article, we review the current results of pro-inflammatory cytokines generated from microglia, postulate its likely function in AD progression, and highlight the recent advances and challenges in targeting pro-inflammatory cytokines for AD therapy. The overall purpose of the present work is to attempt to develop robust and predictive markers, or patterns or clusters of mar- kers, which can be utilized to quantify inflammation in human nutrition studies in the general population. Inflammation is a normal component of host defence, activating the mechanisms involved in pathogen death and protection against various shocks. Thus, in a physiological environment, inflammation is pro- tective. Typically, the inflammatory response is activated fast in response to infection or another stimulus and then follows a time pattern of cellular activation and chemical mediator release. Once the infection or the other insult is eradicated, or at least regulated, mechanisms come into action to terminate inflammation in order to limit additional damage to the host and to commence tissue repair. This process is termed resolution of inflammation, and it is now understood to be an active process involving specific mediators that act to down-regulate the processes that were earlier activated. Fail- ure to resolve inflammation may permit the ordinarily acute inflammatory processes to become chronic. Chronic inflam- mation may also be triggered by continued exposure to the triggering factor. Chronic inflammation is a well-recognised component of many diseases and is a target for several phar- macologic treatments. In order to evaluate the role of diet, foods or specific nutrients on inflammation, it is required to identify possible biomarkers. This review offers a sys- tematic method to discover generic biomarkers of inflam- mation and to explore the factors that may change the status of those biomarkers.

General factor of inflammation

Inflammation is the immune system's response to damaging stimuli, such as pathogens, damaged cells, poisonous substances, or irradiation, and functions by eliminating injurious stimuli and commencing the healing process. Inflammation is consequently a defense mechanism that is crucial to health. Usually, during acute inflammatory reactions, cellular and molecular activities and interactions successfully limit impending harm or infection. This mitigation step contributes to restoration of tissue homeostasis and resolution of the acute inflammation. However, unchecked acute inflammation may become chronic, contributing to a range of chronic inflammatory illness.

At the tissue level, inflammation is characterized by redness, swelling, heat, discomfort, and loss of tissue function, which arise from local immunological, vascular and inflammatory cell responses to infection or injur. Important microcirculatory events that occur during the inflammatory process include vascular permeability alterations, leukocyte recruitment and accumulation, and inflammatory mediator release.

Various pathogenic causes, such as infection, tissue injury, or cardiac infarction, can promote inflammation by producing tissue damage. The etiologies of inflammation can be infectious or non-infectious.

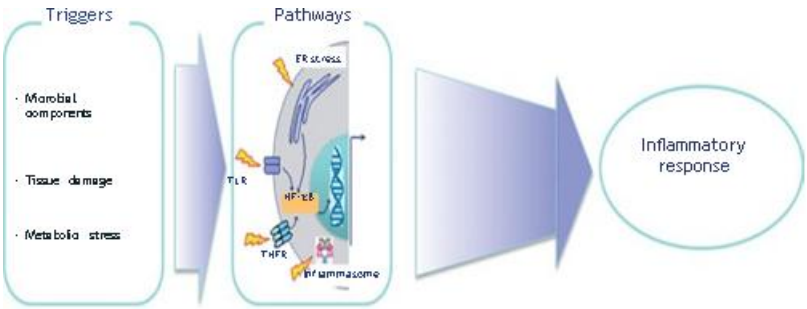

Fig. 1: Schematic overview of the common inflammatory response generated by different causes. Triggers are those factors that can directly begin an inflammatory response. ER, endoplasmic reticulum; TLR, Toll-like receptor; TNFR, TNF receptor.

Prolonged, or chronic, inflammation entails a progressive shift in the type of cells present at the site of inflammation and simultaneous destruction and healing of the tissue due to the ongoing inflammatory process. Inflam- mation may become pathological due to the loss of tolerance and/or of regulatory systems such as resolution. Where this becomes excessive, permanent damage to host tissues and disease can occur (1). Such disorders are distinguished by mark- edly raised quantities of inflammatory markers and of activated

inflammatory cells at the site of tissue injury and in the systemic circulation; this state of inflammation may be regarded as 'high grade'. These disorders include rheumatoid arthritis (RA), inflammatory bowel diseases (IBD), atopic der- matitis, psoriasis and asthma. Chronic inflammation can also be of a 'low grade' and under such circumstances, overt clini- cal manifestations can be minimal or absent; the elevation in the concentrations of inflammatory markers and of inflamma- tory cells in the systemic circulation is not as great as that seen in the frank chronic inflammatory conditions described above. Low-grade asymptomatic inflammation can occur in adipose tissue as a hallmark of obesity. Under these conditions, the adipocyte itself becomes the source of inflammation- related adipokines, while there is also infiltration of adipose tissue by macrophages and T cells, which make major contributions to the inflammatory output Common to both acute and chronic inflammation is that they have an afferent phase, in which the presence of a trigger is sensed by specific types of cells, and an efferent phase, in which an inflammatory response is formed to eradicate the perceived hostile intruder (i.e. the source of the trigger) (i.e. the source of the trigger). Irrespective of the type of inflammation, the response involves four major events. The first event is increased blood flow to the region of inflammation. The second event is enhanced capil- lary permeability mediated by retraction of endothelial cells. This causes bigger molecules, not ordinarily capable of traversing the endothelium, to do so and therefore delivers some soluble mediators to the site of inflammation. The third process is leucocyte migration from the capillaries into the surrounding tissue (Fig. 2). This is fostered by the release of chemo- attractants from the site of inflammation and by the up-regulation of adhesion molecules on the endothelium. Once in the tissue, the leucocytes migrate to the site of inflammation.

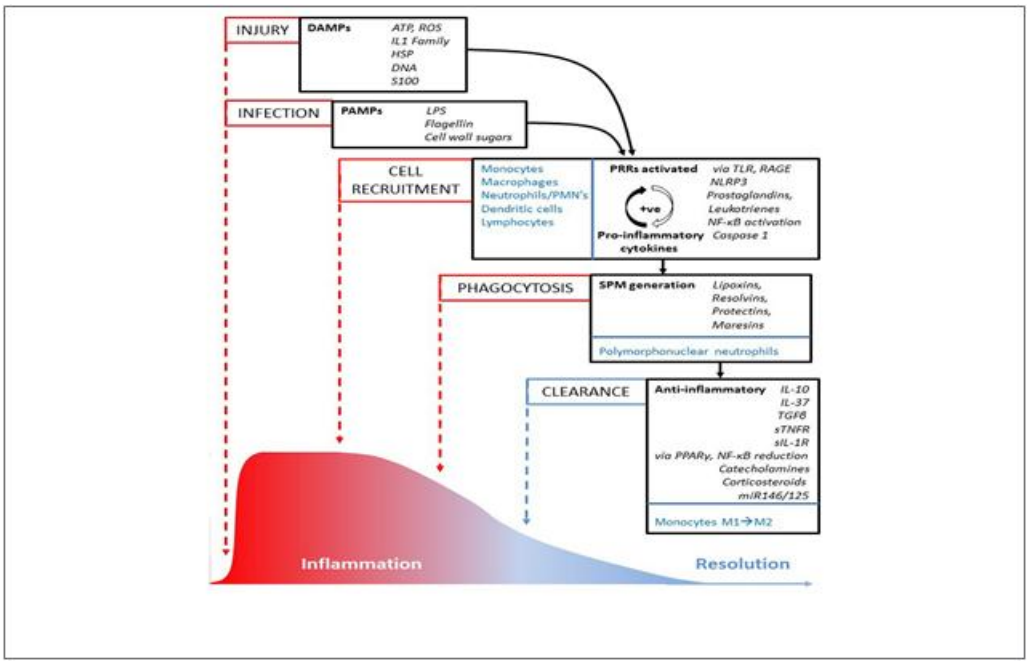

Fig 2: Inflammation road to resolution. An illustration of the sequence of critical events (in uppercase language), cells and chemicals involved in responding to damage or infection, and how the inflammatory episode is resolved over time (from left to right) (from left to right). Cells from the innate and adaptive immune system that are engaged in cell recruitment, phagocytosis, and clearance processes are underlined in blue text; important chemicals are in italic language.

Triggers of Inflammation

Several common molecular pathways have been identified that seem to be associated with both aging and low-grade inflam- mation. These pathways trigger the inflammasome, stimulating NF-κB, and the IL-1β-mediated inflammatory cascade.

Age –Related redox reaction

A redox imbalance has long been associated with aging and led to the development of the redox stress hypothesis of aging. Redox stress is caused by an imbalance between unregu- lated and overproduced reactive oxygen species (ROS) that are produced secondary to mitochondrial energy production, active immunological phagocytic processes, and the prostaglandin pathway through COX enzyme production. While ROS are important molecules regulating numerous physiological and pathological processes in the cell, there is now clear evidence that overproduction of ROS is involved in the development of a number of diseases, such as Alzheimer's disease, rheumatoid, and cardiovascular diseases. Increasing evidence supports the notion that low concentrations of ROS or "primary ROS" are involved in well controlled processes, where their effect on reactive target molecules can be reversible, suggesting that "primary" ROS acts as an important

intracellular signaling molecule. In contrast, the very active OH ROS is less effectively controlled and forms the main damaging type of ROS that is able to react with many macromolecules, such as lipids, proteins, and nucleic acids. This results in DNA oxidation and cell membrane damage, which contributes to the burden of damaged molecules related to aging and age-related diseases.

Mitochondrial ROS

Mitochondria are highly efficient generators of energy, but in doing so they produce ROS. It is estimated that around 90 percent of transferring electrons from cytoplasmic NADPH or the "NOX" catalytic subunit to molecular oxygen. The ROS produced by these enzymes has a crucial function in neutrophils and macrophages as a mechanism for effective bacterial killing and host defense. When the phagocytes recognize an endogenous or exogenous danger signal, the NADPH-oxidase unit translo- cates to fuse with the plasma membrane to create the phagosome. This generates massive amounts of extremely reactive ROS called the phagocytic burst that is particularly effective in killing microorganisms, however phagosomal pH and ion concentration are also believed to be important. Although NOX family of isoenzymes was initially associated with the ROS produced in phagocytes, other members of the NOX family are now known to be involved in a wide range of regulatory roles in many tissues and seem likely to play a role in aging and age-related disorders. Studies in the human vascular system reveal that NOX1, NOX2, and NOX5 increase endothe- lial dysfunction, inflammation, and apoptosis in the vessel walls, but NOX4 by contrast is vasoprotective, by boosting nitric oxide bioavailability. NOX enzymes, therefore, appear to have a role in vascular disease as well as in the maintenance of normal physiological vascular function. Activation of NOX2 and NOX4 occurs in patients with atrial fibrillation and inhibi- tion of NOX by angiotension converting enzyme inhibitor medications or statins has shown useful in preventing post-operative atrial fibrillation.

Identify the biomarker of inflammation

Inflammation has long been considered to play a crucial part in the pathology of a number of human diseases, including RA,psoriasis, Crohn's disease, allergic asthma and atopic dermati- tis, being centrally implicated in the tissue damage that is seen. These disorders with a well-recognised inflammatory component are frequently treated with general or particular anti- inflammatory medicines with the aim of eliciting a clini- cal benefit. More recently, it has been obvious that metabolic disorders such as atherosclerosis, type 2 diabetes and obesity have an inflammatory component albeit low-grade; nevertheless, the amount to which this is causal in the pathology is not yet clear. These disorders are not routinely treated with anti-inflammatory medicines. It is assumed that several dietary components can influence many elements of inflam- mation consequently, nutrition may have a role in predisposing to illnesses that have an inflammatory component and altered nutrition may be effective in the prevention or treatment of such disorders In order to understand the role of diet or its component foods.

A biomarker is described as 'a trait that is objectively tested and analyzed as an indicator of normal biological processes, pathogenic processes, or phar- macologic reactions to an intervention. However, clear guidelines on which biomarkers to employ and how to interpret patterns of biomarkers and changes in biomarkers in the context of inflammation are absent. The Institute of Medicine recently presented a comprehensive approach for identifi- cation of biomarkers and surrogate endpoints in chronic diseases. The Institute of Medicine proposed basing the evaluation procedure for biomarkers on three steps:

(1) Analytical validation of the biomarker (reference range, accuracy, limits of detection, reproducibility, etc.);
(2) Qualification of the available evidence on an association between the biomarker and disease states including data showing the effects of an intervention on both the biomarker and clinical outcomes;
(3) Usage of a utilisation stage that largely includes the decision of whether analytical validation and qualification undertaken give sufficient support for the planned use of the biomarker The overarching purpose of this review is to find robust and predictive markers, or patterns or clusters of markers, that may be used to measure inflammation in human nutrition research in the general popu- lation and to build a consensus for grading these biomarkers.

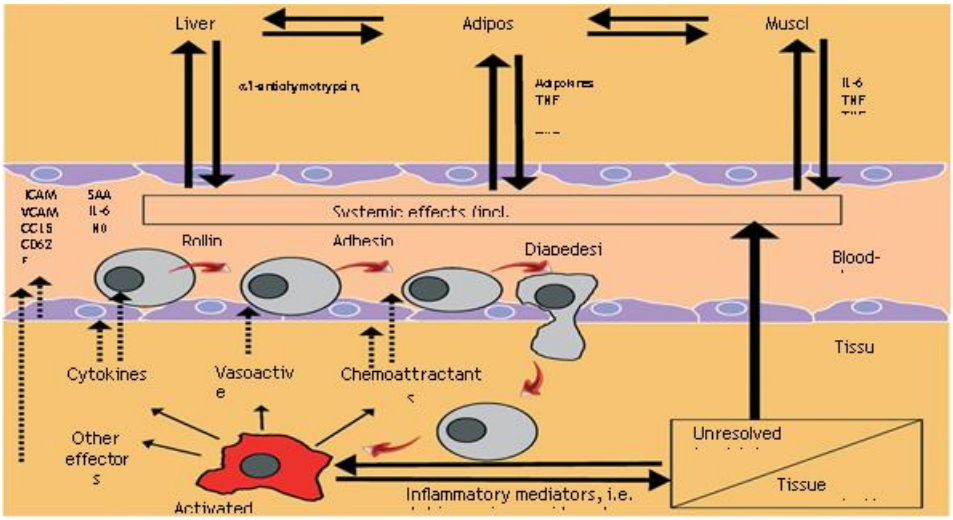

Fig. 3: C, complement; CRP, C-reactive protein; SAA, serum amyloid A; TNFR, TNF receptor; ra, receptor antagonist; PAI, plasmi- nogen activator inhibitor; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; CCL, chemokine (C– C motif) ligand; CD62E, E-selectin endothelial leukocyte adhesion molecule 1; CD62P, P-selectin endothelial leukocyte adhesion molecule 1; CXCL, chemokine (C– X– C motif) ligand; tPA, tissue plasminogen activator; vWF, von Willebrand factor; IFN, interferon; PLA, phospholipase A; ROS, reactive oxygen species.

Table 1: Lipid mediator associated with inflammation.

Class	Mediator	Substrate	Receptor(s)
Prostanoids	PGD_2 PGE_2 PGF_{2a}	Arachidonic acid via COX	DP1, DP2
	PGI_2 TXA_2	Arachidonic acid via COX	EP1, EP2, EP3, EP4FP
	$PGE_1PGD_3PGE_3$	Arachidonic acid via COX	IP TP
	5-HETE	Arachidonic acid via COX Dihomo-g-linolenic acid via COX	EP1, EP2, EP3, EP4 DP1, DP2
Leukotrienes		EPA via COX	EP1, EP2, EP3, EP4
		EPA via COX	BLT2
		Arachidonic acid via 5-LOX	
	5-HPETE	Arachidonic acid via 5-LOX	OXE
	LTB_4	Arachidonic acid via 5-LOX	BLT1, BLT2
	LTC_4, D_4, E_4 (termed cys-LT)15-HETE	Arachidonic acid via 5-LOX Arachidonic acid via 15-LOX	CysLT1, CysLT2BLT2
	15-HPETE	Arachidonic acid via 15-LOX	BLT2
	12-HETE	Arachidonic acid via 12-LOX	BLT2
Lipoxins	LTB_5LXA_4	EPA via 5-LOX	BLT1, BLT2FPR2/ALX
		Arachidonic acid via 15-LOX and 5-LOX or 5-LOX	

Microbiota associated with markers

As discussed earlier, microbiota and, particularly, gut micro- biota might play an important role in human health and physiopathology. It is possible that circulating traces of trans- located bacteria or bacterial components could be used as biomarkers to predict metabolic disease risk in humans. Measurements of blood LPS have frequently been reported in the literature as a feature of mucosal barrier failure. How- ever, such measures are rather unspecific, are limited to Gram-negative organisms and pose some technical difficulties. Alternative methods to detect material of bacterial origin or to detect responses to specific organisms are emerging. Indeed, a battery of antibodies against different bacterial antigens is currently under investigation, although their physiological role is still unclear. In addition, specific bacterial 16S ribosomal DNA detection by PCR amplification in blood is a tool being used more frequently. The combination of excellent sensitivity and specificity, ease and speed has made real-time PCR technology an appealing alternative to conventional culture-based testing methods. This approach has been used recently to show a positive association between 16S ribosomal DNA in blood and diabetes onset. The 16S ribosomal DNA concentration was analysed in blood in a cohort of 3280 subjects without diabetes or obesity. Baseline 16S ribosomal DNA level was higher in those subjects who developed diabetes by the 9-year follow-up.

Future prospective

Aging is varied across humans and highly changeable

amongst different organs and tissues. Our genes, our lifestyles, and our response to stress are infinitely individual and varied, so that the immunobiography of each person tells a different story of how each will respond to the internal and external environmental stressors. But evidence is mounting suggesting the aging process may be changeable.

Because aging is the biggest risk factor for age-related disorders, understanding age better and safeguarding the health of older peo- ple and societies is highly important personally and for societies and governments. Knowledge on the underlying biological pathways and the genetic and life-style mechanisms linked with age-related disease and aging itself is increasing. Evidence from centenarian and nonagenarian studies suggests that these oldest people of populations have had the ability to prevent aging and age-related disorders Other studies show that cente- narians may demonstrate optimal cardiovascular risk factors or have either instinctively or through social example, adopted lifestyles which have interacted with their genes to facili- tate a healthy aging phenotype. Population studies across the world suggest that the age-specific incidence of cardiovascular disease, stroke, and dementia is decreasing.. This shows that better blood pressure and diabetes management and statin use may directly or indirectly link into and downregulate cellular pathways related with inflammation. Research into how carriage of certain gene alleles, such as TCF7L2 or IL-6 can increase inflammation or stroke risk, respec- tively, and can be ameliorated by following a Mediterranean-type diet, or how gene splicing and features of senescence may be modulated by resveratrol in food herald research into how gene, diet, and lifestyles can interact, with positive or negative effects on the immune system and health. Increased knowledge is emerging as to how epigenetic modulation might influence cytokine genes with evidence relating cytokine epigenetic modification to neuro inflammatory. Obesity, smoking, and malnutrition have been proven to have next generational epigenetic consequences, and seem likely to contribute to the propensity of offspring developing age-related disease or conversely the longevity phenotype.

Other tactics should be devised which link with public health messaging and urge people to embrace behavioral adjustments in lifestyles. Modifications should include: changes in diets to incorporate more omega-3 containing foods or fruits and vegetables as in the Mediterranean diet engagement in regular controlled exercise routines ongoing participation with social connections and intellectual pursuits in daily lives or best of all a combination of life-style elements, all of which have been found to lower the inflammatory profile and improve the quality of aging. Although the role of diet on human health and connections through nutrition, inflammation, and cancer are not as linear as those between tobacco, smoking, and lung cancer, obesity is linked to chronic inflammation through several mechanisms,including the dysregulation of autophagy, whereas fasting has anti- inflammatory effects, similar to the effect of exercise, and may downregulate inflammatory biomarkers. There is, therefore, substantial interest in the involvement of the intestinal micro- biota and health and the so-called immune-relevant microbiome with important correlations between inflammation and neurodegenerative disease, bacterial β-hydroxybutyrate metabolites, and the role of vagal stimulation. Increasing data reveals that multiple signaling pathways are activated in a stress-type-dependent fashion, and all appear to converge with nuclear factor (NF)-κB signaling, which is a fundamental controller of the immune response, and inflammatory cascade With increasing age, immune homeo- stasis loosens, NF-κB signaling becomes less tightly controlled or is more readily triggered, cytokine dysregulation occurs, and a pro-inflammatory phenotype predominates that underpins most major age-related diseases from atherosclerosis to cancer, and aging itself Understanding how different stimuli trigger the NF-κB cascade is an important area of research. In animal models, miRNA-based regulatory networks involving miR-155 and miR-146a, tightly regulate NF-κB activity, with miR-146a downregulating and miR-155 upregulating NF-κB expression. There is a crucial temporal separation of miR-155 and miR-146a cellular expression that allows finely controlled NK-κB signaling and enables a precise macrophage inflammatory response, which needs additional exploration.

Therapeutic options may develop through better under-sight of the molecular pathways that promote senesce cells and SASP in the cellular settings of chronic disease or whether senescent cells can be eliminated by upregulating autophagy and using sophisticated tagging techniques. There will be increased opportunities to use the knowledge gained from clini- cal studies in autoimmune disease, about the roles and actions of monoclonal antibodies in modulating inflammation, which may be able to be utilized in treatments for other age-related diseases involving inflammation . The formulations of new and more specialized medications are likely to become available as the modes of action of kinases, such an AMPK and mTOR which govern the senescence and inflammation pathways, become better understood. Old medications, such as metformin, still used in diabetes care, are being repurposed and have been found to have exciting new uses through their capacity to modulate epigenetic gene expression. Clinical investigations are undertaken to determine any modifying effect of metformin in aging and age-related illnesses. The use of his- tone deacetylating medications is predicted to rise as the clinical usage of deacetylation and methylation agents is explored in cancer with increased knowledge of their effects and safety requirements. The current interest in diet and modified diets will encourage further studies assessing how nutrachemicals modify gene expression, for example, through the regulation of intracellular receptors that bind

the promoters of certain genes, and may help to design more specific drugs to modify metabolism and benefit health.

CONCLUSION

There is an urgent demand for accurately monitoring inflamma- tory status in the context of disease and actions to pre- vent or treat disease, including dietary modification. Currently, recommendations on how to appropriately diagnose inflam- mation are inadequate. To monitor inflammation in a meaningful way, the markers utilized must be genuine; that is, they must reflect the inflammatory process under research and they must be pre- dictive of future health status. Inflammation per se is a normal, vital, complex physiological process crucial for healing and maintaining health. This process involves many cells and mediators. The latter contain various pep- tides and proteins that circulate in the bloodstream (e.g. cyto- kines, chemokines, soluble versions of adhesion molecules and acute-phase proteins). These are involved in, or created as a result of, the inflammatory process independent of its trigger and its location. Thus, they are common to all inflammatory illnesses, to acute and chronic inflammatory reactions and to both high-grade and low-grade inflammation.

The focus in inflammation research has been very much on such pro-inflammatory mar- kers that are part of an amplification cascade or that induce tissue damage, and the factors that control these and which can be used to identify illness. There has been less emphasis on anti-inflammatory markers, which include receptor antagonists, soluble versions of receptors, cytokines and lipid mediators that act to down-regulate the production of inflammatory mediators. There is considerably less understanding of those elements that terminate (resolve) inflammation. Cur- rently, there is no consensus on whether markers of inflam- mation best characterize low-grade inflammation or can differentiate between acute and chronic inflammation or among the initiation, propagation and resolution phases of inflammatory responses. For most inflammatory markers, there is insufficient evidence on the predictive usefulness of (differ- ences in or changes in) their concentration from prospective research; that is, information on their role as (independent) markers of disease risk and outcome is mainly sparse. Many modifying factors affect the concentration of an inflammatory marker at a given time; the effects of some factors, such as age, physical (in)activity and smoking, on a small number of inflammatory markers are well described, but the effects of these factors on the range of markers considered here are mostly not known. In particular, information of the impacts of genotype, sex and gut microbiome is sparse.

REFERENCE

1. Ter Horst R, Jaeger M, Smeekens SP, Oosting M, Swertz MA, Li Y, et al. Host and environmental factors influencing individual human cytokine responses. Cell., 2016; 167(4): 1111e–24e. doi:10.1016/j.cell.2016.10.018.
2. Govindaraju D, Atzmon G, Barzilai N. Genetics, lifestyle and longevity: lessons from centenarians. Appl Transl Genom, 2015; 4: 23–32. doi:10.1016/j. atg.2015.01.001.
3. Rea JNM, Carvalho A, McNerlan SE, Alexander HD, Rea IM. Genes and life-style factors in BELFAST nonagenarians: nature, nurture and narrative. Biogerontology, 2015; 16(5): 587–97. doi:10.1007/s10522-015-9567-y.
4. Liu Y-Z, Wang Y-X, Jiang C-L. Inflammation: the common pathway of stress-related diseases. Front Hum Neurosci, 2017; 11: 316. doi:10.3389/ fnhum.2017.00316.
5. Abe K, Hashimoto Y, Yatsushiro S, Yamamura S, Bando M, Hiroshima Y, et al. Simultaneous immunoassay analysis of plasma IL-6 and TNF-α on a microchip. PLoS One, 2013; 8(1): e53620. doi:10.1371/journal.pone.0053620.
6. Battle A, Khan Z, Wang SH, Mitrano A, Ford MJ, Pritchard JK, et al. Genomic variation. Impact of regulatory variation from RNA to protein. Science, 2015; 347(6222): 664–647. doi:10.1126 /science.1260793.
7. Kubiczkova L, Sedlarikova L, Hajek R, Sevcikova S. TGF-beta – an excellent serv- ant but a bad master. J Transl Med, 2012; 10: 183. doi:10.1186/1479-5876-10-183 Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci., 2000; 908: 244–54. doi:10.1111/j.1749-6632.2000.tb06651.x
8. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, et al. Inflammaging and antiinflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev., 2007; 128: 92–105. doi:10.1016/j.mad.2006.11.016.
9. Medzhitov R. Origin and physiological role of inflammation. Nature, 2008; 454: 428–35. doi:10.1038/nature07201
10. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci., 2014; 69(Suppl 1): S4–9. doi:10.1093 /gerona/glu057.
11. Chung HY, Cesari M, Anton S, Marzetti E, Giovannini S, Seo AY, et al. Molecular inflammation: underpinnings of aging and age-related diseases. Ageing Res Rev., 2009; 8(1): 18–30. doi:10.1016/j.arr.2008.07.002.
12. Martin SJ. Cell death and inflammation: the case for IL-1 family cytokines as the canonical DAMPs of the immune system. FEBS J., 2016; 283(14): 2599–615. doi:10.1111/febs.13775 Kumar V, Abbas A, Aster J. Robbins & Cotran Pathologic Basis of Disease. IX ed. Amsterdam: Elsevier, 2014.
13. Nathan C. Points of control in inflammation. Nature, 2002; 420(6917): 846–52. doi:10.1038/nature01320.

14. Chiurchiù V, Leuti A, Maccarrone M. Bioactive lipids and chronic inflam- mation: managing the fire within. Front Immunol, 2018; 9: 38. doi:10.3389/ fimmu.2018.00038.
15. Serhan CN, Chiang N, Dalli J, Levy BD. Lipid mediators in the resolution of inflammation. Cold Spring Harb Perspect Biol, 2015; 7(2): a016311. doi:10.1101/cshperspect.a016311.
16. Serhan CN, Chiang N, Dalli J. New pro-resolving n-3 mediators bridge resolution of infectious inflammation to tissue regeneration. Mol Aspects Med, 2017. doi:10.1016/j.mam.2017.08.002.
17. Serhan CN. Pro-resolving lipid mediators are leads for resolution physio- logy. Nature, 2014; 510(7503): 92–101. doi:10.1038/nature134.
18. Awad F, Assrawi E, Jumeau C, Georgin-Lavialle S, Cobret L, Duquesnoy P, et al. Impact of human monocyte and macrophage polarization on NLR expression and NLRP3 inflammasome activation. PLoS One, 2017; 12(4): e0175336. doi:10.1371 /journal.pone.0175336.
19. Mantovani A, Biswas SK, Galdiero MR, Sica A, Locati M. Macrophage plasticity and polarization in tissue repair and remodelling. J Pathol, 2013; 229: 176–85. doi:10.1002/path.4133.
20. Kittan NA, Allen RM, Dhaliwal A, Cavassani KA, Schaller M, Gallagher KA, et al. Cytokine induced phenotypic and epigenetic signatures are key to esta- blishing specific macrophage phenotypes. PLoS One, 2013; 8(10): e78045. doi:10.1371 /journal.pone.0078045.
21. Chiurchiù V, Leuti A, Dalli J, Jacobsson A, Battistini L, Maccarrone M, et al. Proresolving lipid mediators resolvin D1, resolvin D2, and maresin 1 are critical in modulating T cell responses. Sci Transl Med, 2016; 8: 353ra111.1. doi:10.1126 /scitranslmed.aaf7483.
22. Krishnamoorthy N, Burkett PR, Dalli J, Abdulnour RE, Colas R, Ramon S, et al. Cutting edge: maresin-1 engages regulatory T cells to limit type 2 innate lymphoid cell activation and promote resolution of lung inflammation. J Immunol, 2015; 194(3): 863–7. doi:10.4049/jimmunol.1402534.
23. Ramon S, Gao F, Serhan CN, Phipps RP. Specialized proresolving mediators enhance human B cell differentiation to antibody-secreting cells. J Immunol, 2012; 189: 1036–42. doi:10.4049 /jimmunol.1103483.
24. Recchiuti A, Serhan CN. Pro-resolving lipid mediators (SPMs) and their actions in regulating miRNA in novel resolution circuits in inflammation. Front Immunol, 2012; 3: 298. doi:10.3389 /fimmu.2012.00298.
25. Fredman G, Hellmann J, Proto JD, Kuriakose G, Colas RA, Dorweiler B, et al. An imbalance between specialized pro-resolving lipid mediators and pro- inflammatory leukotrienes promotes instability of atherosclerotic plaques. Nat Commun, 2016; 7: 2859. doi:10.1038/ncomms1285.
26. Spite M, Norling LV, Summers L, Spite M, Norling LV, Summers L, et al. Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. Nature, 2009; 461(7268): 1287–91.
27. Buckley CD, Gilroy DW, Serhan CN. Pro-Resolving lipid mediators and mechanisms in the resolution of acute inflammation. Immunity (2014) 40(3):315–27. doi:10.1016/j.immuni.2014.02.009
28. Arita M, Ohira T, Sun YP, Elangovan S, Chiang N, Serhan CN. Resolvin E1 selectively interacts with leukotriene B4 receptor BLT1 and ChemR23 to reg- ulate inflammation. J Immunol, 2007; 178: 3912–7. doi:10.4049/jimmunol. 178.6.3912.
29. Liao Z, Dong J, Wu W, Yang T, Wang T, Guo L, et al. Resolvin D1 attenuates inflammation in lipopolysaccharide-induced acute lung injury through a process involving the PPARgamma/NF-kappaB pathway. Respir Res, 2012; 13: 110. doi:10.1186/1465-9921-13-110.
30. Chatterjee A, Sharma A, Chen M, Toy R, Mottola G, Conte MS. The pro- resolving lipid mediator maresin 1 (MaR1) attenuates inflammatory signaling pathways in vascular smooth muscle and endothelial cells. PLoS One, 2014; 9(11): e113480. doi:10.1371/journal.pone.0113480.
31. Marcon R, Bento AF, Dutra RC, Bicca MA, Leite DF, Calixto JB. Maresin 1, a proresolving lipid mediator derived from omega-3 polyunsaturated fatty acids, exerts protective actions in murine models of colitis. J Immunol, 2013; 191: 4288–98. doi:10.4049/jimmunol.1202743.
32. Perretti M, Norling LV. Actions of SPM in regulating host responses in arthritis. Mol Aspects Med, 2017; 58: 57–64.1. doi:10.1016/j.mam.2017. 04.005.
33. Sulciner ML, Serhan CN, Gilligan MM, Mudge DK, Chang J, Gartung A, et al. Resolvins suppress tumor growth and enhance cancer therapy. J Exp Med, 2018; 215(1): 115–40. doi:10.1084/jem.20170681.
34. Fiala M, Terrando N, Dalli J. Specialized pro-resolving mediators from omega-3 fatty acids improve amyloid-β phagocytosis and regulate inflam- mation in patients with minor cognitive impairment. J Alzheimers Dis., 2015; 48: 293–301.1. doi:10.3233/JAD-150367.
35. Zhu M, Wang X, Hjorth E, Colas RA, Schroeder L, Granholm A-C, et al. Pro-resolving lipid mediators improve neuronal survival and increase Aβ42 phagocytosis. Mol Neurobiol, 2016; 53: 2733–49. doi:10.1007/s12035-015- 9544-0.
36. Skoldstam L, Hagfors L, Johansson G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. Ann Rheum Dis., 2003; 62(3): 208–14. doi:10.1136/ard.62.3.208.
37. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart dis- ease and stroke in women. Circulation, 2009; 119(8): 1093–100. doi:10.1161/ Circulationaha. 108.816736.

38. Esposito K, Maiorino MI, Bellastella G, Chiodini P, Panagiotakos D, Giugliano D. A journey into a Mediterranean diet and type 2 diabetes: a systematic review with meta-analyses. BMJ Open, 2015; 5: e008222. doi:10.1136/ bmjopen-2015-008222.
39. Demarin V, Lisak M, Morović S. Mediterranean diet in healthy lifestyle and prevention of stroke. Acta Clin Croat, 2011; 50(1): 67–77.
40. Corella D, Carrasco P, Sorlí JV, Estruch R, Rico-Sanz J, Martínez-González MÁ, et al. Mediterranean diet reduces the adverse effect of the TCF7L2-rs7903146 polymorphism on cardiovascular risk factors and stroke incidence: a ran- domized controlled trial in a high-cardiovascular-risk population. Diabetes Care, 2013; 36: 3803–11. doi:10.2337/dc13-0955.
41. Harman D. Aging: a theory based on free radical and radiation chemistry.
42. J Gerontol, 1956; 11: 298–300. doi:10.1093 /geronj/11.3.298.
43. Bedard K, Krause KH. The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiol Rev., 2007; 87: 245–313. doi:10.1152/physrev.00044.2005.
44. Daiber A. Redox signaling (cross-talk) from and to mitochondria involves mitochondrial pores and reactive oxygen species. Biochim Biophys Acta, 2010; 1797(6–7): 897–906. doi:10.1016 /j.bbabio.2010.01.032.
45. Marcus RL, Addison O, Kidde JP, Dibble LE, Lastayo PC. Skeletal muscle fat infiltration: impact of age, inactivity, and exercise. J Nut Health Aging, 2010; 14: 362–6. doi:10.1007/s12603-010-0081-2.
46. Rea IM. Towards ageing well: use it or lose it: exercise, epigenetics and cog- nition. Biogerontology, 2017; 18(4): 679–91. doi:10.1007/s10522-017-9719-3.
47. Diot A, Morten K, Poulton J. Mitophagy plays a central role in mitochondrial ageing. Mamm Genome, 2016; 27: 381–95. doi:10.1007/s00335-016-9651-x.
48. Sohal RS, Orr WC. The redox stress hypothesis of aging. Free Radic Biol Med, 2012; 52(3): 539–55. doi:10.1016/j.freeradbiomed.2011.10.445.
49. Takac I, Schroder K, Brandes RP. The Nox family of NADPH oxidases: friend or foe of the vascular system? Curr Hypertens Rep, 2012; 14: 70–8. doi:10.1007/s11906-011-0238-3.
50. Babior BM, Lambeth JD, Nauseef W. The neutrophil NADPH oxidase. Arch Biochem Biophys, 2002; 397(2): 342–324. doi:10.1006 /abbi.2001.2642
51. Nguyen GT, Green ER, Mecsas J. Neutrophils to the ROScue: mechanisms of NADPH oxidase activation and bacterial resistance. Front Cell Infect Microbiol, 2017; 7: 373. doi:10.3389/fcimb.2017.00373.
52. Drummond GR, Sobey CG. Endothelial NADPH oxidases: which NOX to target in vascular disease? Trends Endocrinol Metab, 2014; 25(9): 452–63. doi:10.1016/j.tem.2014.06.012.
53. Youn J-Y, Zhang J, Zhang Y, Chen H, Liu D, Ping P, et al. Oxidative stress in atrial fibrillation: an emerging role of NADPH oxidase. J Mol Cell Cardiol, 2013; 62: 72–9. doi:10.1016 /j.yjmcc.2013.04.019.
54. Marnett LJ, Rowlinson SW, Goodwin DC, Kalgutkar AS, Lanzo CA. Arachidonic acid oxygenation by COX-1 and COX-2. Mechanisms of catalysis and inhibition. J Biol Chem, 1999; 274: 22903–6. doi:10.1074/jbc. 274.33.22903.