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REVIEW ARTICLE

Dietary Technologies to Optimize Healing from Injury-Induced Inflammation

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Abstract: Inflammation is an acute adaptive response to injury. However, if the initial inflammatory response to an injury is not completely healed, it becomes chronic low-level inflammation that is strongly associated with many chronic disease states, including metabolic (obesity and diabetes), cardiovascular, auto-immune, and neurogenerative disorders as well as cancer. The healing process is far more complex than the initiation of inflammation. Within that complexity of healing is a sequence of events that are under profound dietary control and can be defined by specific blood markers. Those molecular events of the healing process that are under significant dietary control are termed as the Resolution Response. The purpose of this review is to describe the molecular components of the Resolution Response and how different dietary factors can either optimize or inhibit their actions. In particular, those dietary components that optimize the Resolution Response include a calorie-restricted, protein-adequate, moderate-carbohydrate, low-fat diet referred to as the Zone diet, omega-3 fatty acids, and polyphenols. The appropriate combination of these dietary interventions constitutes the foundation of Pro-Resolution Nutrition. The effect of these dietary components the actions of NF-κB, AMPK, eicosanoids, and resolvins are described in this review, as well as ranges of appropriate blood markers that indicate success in optimizing the Resolution Response by dietary interventions.

Keywords: Resolution Response, inflammation, Zone diet, omega-3 fatty acids, polyphenols, NF-κB, AMPK, eicosanoids, resolvins.

1. INTRODUCTION

At the molecular level, all chronic diseases are initially driven by chronic low-level unresolved inflammation, which is below the perception of pain. Such inflammation is a consequence of the blockage of the body's natural healing response to injury-induced inflammation [1]. The Resolution Response is that part of the healing process that is under profound dietary control and can be defined by specific blood markers.

New insights into the molecular biology of the Resolution Response has led to the development of a comprehensive nutritional program that is personalized to maximize the individual's healthspan, which is defined as longevity minus years of disability. This dietary program is termed Pro-Resolution Nutrition and represents a comprehensive, personalized dietary pathway to simultaneously achieve improved treatment of existing chronic conditions, as well as extending one's healthspan. Such personalization is possible since each molecular component of the Resolution Response can be precisely modulated, based on validated blood markers of the specific dietary components of Pro-Resolution Nutrition.

2. RESOLUTION RESPONSE THEORY OF CHRONIC DISEASES

The history behind the concept of the Resolution Response theory of chronic diseases started more than 150 years ago, with the development of Louis Pasteur's germ theory [2,3]. While the germ theory was an excellent matrix for describing how

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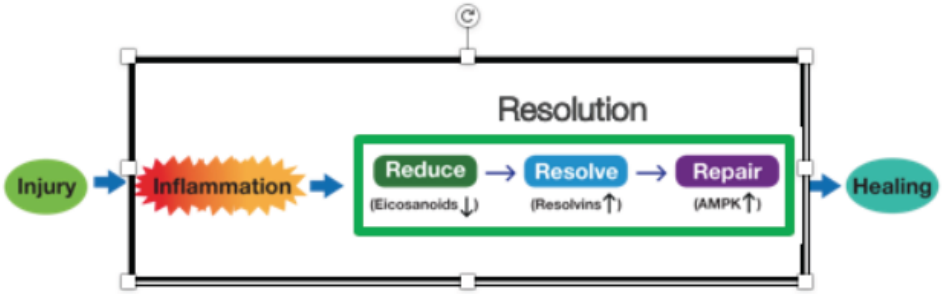

Fig. (1). The basic flow of the hormonal changes (eicosanoids and resolvins) and the activation of AMPK required for the resolution of an injury leading to healing.

bacteria and viruses cause infectious disease, it has not yet proved useful for understanding the causes of chronic diseases.

Chronic diseases are different than infectious. Chronic diseases are considered to be idiopathic. This means that, unlike infectious diseases that have a defined cause, chronic diseases are of unknown origin.

The beginning of the development of the Resolution Response theory of chronic disease began with the awarding of the 1982 Nobel Prize in medicine to Sune Bergstrom, Bengt Samuelsson and John Vane for understanding the role of a group of pro-inflammatory hormones known as eicosanoids as major players in the initiation of inflammation [4]. This led to an appreciation of the role of nutrition in inflammation since eicosanoid levels can ultimately be modulated by the diet.

Continued research into the role of diet and inflammation has expanded from this starting point to understand it is not inflammation *per se* that is the cause of chronic disease, but the blockage of the body's internal healing response to tissue damage caused by chronic unresolved inflammation that is the underlying driving force for the development of a chronic disease. Just like eicosanoids, the Resolution Response, which is the body's key internal component in healing, can also be modulated by the diet.

3. UNDERSTANDING INFLAMMATION AND RESOLUTION

Inflammation can be best understood as a double-edged sword. There is a need for enough inflammation to combat microbial invasions and address physical injuries to keep us alive. However, unless that inflammation is resolved, the damage to the tissue caused by the initial injury will not completely heal. In other words, some inflammation is needed to survive, but the damage caused by the initial inflammation has to be reduced, resolved, and repaired, to remain well and thus, significantly delay the development of a chronic disease. This flow from injury-induced inflammation to healing is shown in Fig. (**1**).

Both inflammation and resolution are quiescent parts of the overall inflammatory response unless activated by an injury. Injuries activate inflammation, which, in turn, activates the resolution. Furthermore, inflammation and resolution represent separate active pathways of an overall balanced inflammatory response [5]. This constant balancing act between the molecular pathways that control injury-induced inflammation and its eventual healing can best be summarized in Fig. (**2**) that describes this intricate orchestration in the form of a biological gyroscope.

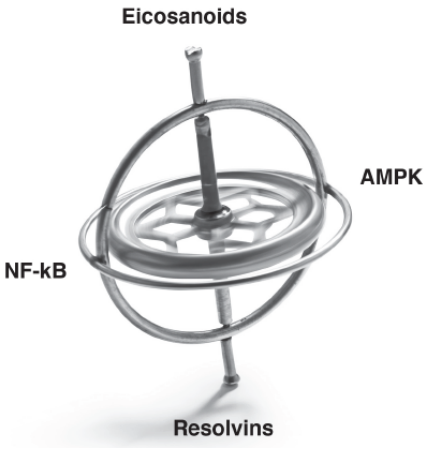

Fig. (2). Illustration of the balancing of the molecular factors involved in the Resolution Response.

The gene transcription factor NF-κB is the genetic master switch for turning on inflammation [6,7]. This is because NF-κB controls the genera-

tion of inflammatory cytokines as well as increases the levels of the COX-2 enzyme that produces many of the pro-inflammatory eicosanoids. Eicosanoids are the hormonal agents that enhance the intensity of inflammation. On the other hand, resolvins are the hormones that are necessary to turn off (*i.e.*, resolve) inflammation, and are only activated by inflammation [8]. In addition, resolvins enhance the body's ability to kill and clear microbial infections (both bacterial and viral) [9-11]. Finally, AMPK is the body's primary sensor of both energy and glucose, and acts as the master switch for tissue repair by activating various gene transcription factors that promote the regeneration of the damage caused by initial inflammation as well as inhibiting NF-κB [12-14]. Once NF-κB becomes quiescent, inflammatory homeostasis is re-established in the tissue until the next random injury.

As long as these master switches (NF-κB and AMPK) and hormones (eicosanoids and resolvins) are maintained in balance, an appropriate zone of inflammation can be maintained. This allows the optimal healing response from any injury.

The Resolution Response is highly orchestrated and sequential in time. The inflammation caused by an injury must be sufficiently reduced before the resolvins can eliminate any residual inflammation. It is only after the resolution of inflammation is completed that activation of AMPK can take place to bring about the full potential for repair of the tissue damage to successfully complete the healing process. The Resolution Response can be viewed as a systems-based response in which each molecular component must accomplish the assigned task before being passed to the next molecular component of the Resolution Response.

4. INJURIES THAT CAUSE INFLAMMATION

The types of injuries that can cause an initial inflammatory response are quite extensive, and are listed below:

- Physical injuries (internal and external)
- Microbial invasions
- Diet-induced
- Oxidative stress-induced
- Surgery-induced
- Drug-induced (cancer drugs in particular)
- Stressor-induced (physical, emotional, and environmental)

This shows that the original injury may no longer be present in the body, but the lack of resolution of the inflammation generated from that initial injury can continue to produce new types of inflammatory damage.

5. HOW CHRONIC DISEASE DEVELOPS

Unlike infectious diseases, chronic diseases take years, if not decades, to develop. This is because a chronic disease is often the consequence of long-term accumulated organ damage caused by a blocked Resolution Response. Furthermore, this initial unresolved inflammation can be maintained by constant diet-induced injuries. The initial injury that caused tissue damage may have left the body many years earlier, but the incomplete healing of that initial inflammatory damage caused by a constantly blocked Resolution Response which continues to build until there is enough accumulated organ damage to be considered a chronic disease. Now the individual will usually require long-term use of medication to treat the symptoms of that particular chronic disease (as well as other comorbidities) that started years, if not decades, earlier with a blocked Resolution Response that continued to the present time.

6. CONSEQUENCES OF A BLOCKED RESOLUTION RESPONSE

The first consequence of a blocked Resolution Response is the build-up of unresolved chronic inflammation with increased levels of pro-inflammatory mediators, such as cytokines and eicosanoids, generated by continued low-level activation of NF-κB. These inflammatory mediators can disrupt hormonal signaling patterns as well as reduce the efficiency of both the innate and adaptive immune systems [15, 16]. This disruption of the innate immune system is the first step leading to the generation of more insidious and more permanent consequences of a blocked Resolution Response. These include the development of senescent cells and the acceleration of fibrosis, coupled with a compromised immune system with a reduced ability to remove senescent cells and fibrotic tissue from the body due to the presence of high levels of unresolved inflammation [17, 18]. How unresolved inflammation leads to the earlier development of a chronic disease is illustrated in Fig. (**3**).

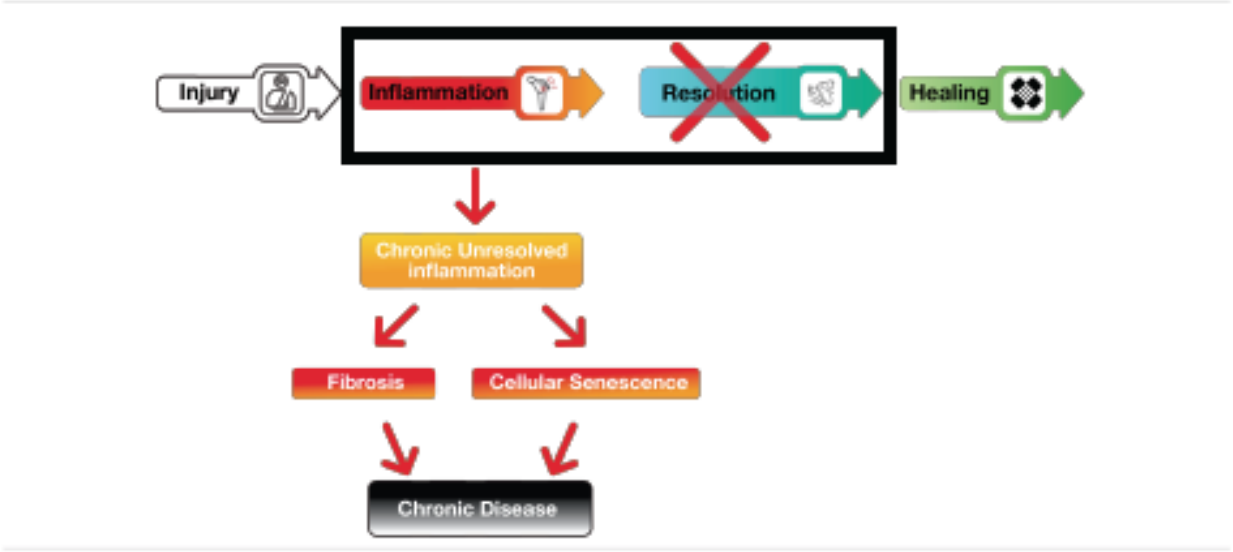

Fig. (3). When the Resolution Response is inhibited, inflammation caused by an injury cannot be completely resolved, and as a result, there is an increase in unresolved inflammation. Eventually, the compounding levels of unresolved inflammation will lead to the development of either cellular senescence or fibrosis that will accelerate the development of a chronic disease.

7. CELLULAR SENESCENCE

One consequence of a blocked Resolution Response is the generation of senescent cells. Cellular senescence is a natural biological mechanism in which a cell permanently halts its division due to stressors on its genes [19]. Such senescent cells remain metabolically active, but become incapable of further growth. Cellular senescence is the primary internal process the body utilizes to prevent tumor growth. However, cellular senescence can be induced by a diverse number of other external stressors causing DNA damage, including drug-induced (especially cancer drugs), radiation, oxidative stress, mitochondrial dysfunction, and elevated glucose levels caused by insulin resistance. Whatever the cause, once a cell becomes senescent, it begins secreting large quantities of inflammatory mediators (including cytokines generated by NF-κB) that disrupt the local microenvironment of the tissues [20]. This collection of inflammatory mediators is termed the Senescence Associated Secretory Phenotype or SASP. With a fully functional immune response, these inflammatory signals would normally act as beacons calling for the elimination of the senescence cells. However, excess unresolved inflammation can overwhelm the immune system so that it doesn't recognize these signals as effectively [21]. The result is that the senescent cells are not eliminated, and now become a permanent new source of continuous inflammation within the injured tissue. In addition to its adverse effects on tissue function, the SASP also contains factors that can induce the development of senescence in neighboring cells [22]. This growing population of senescent cells sets off a cascade of inflammatory events that culminates in the generation of an increasingly dysfunctional organ that underlies the development of virtually all types of chronic diseases. It is becoming recognized that chronic diseases associated with aging (metabolic conditions, such as obesity and diabetes, heart disease, cancer, auto-immune, ocular, neurodegenerative, *etc*.) are strongly associated with increased levels of senescent cells in the affected organs [23].

8. FIBROSIS

Just as cellular senescence is essential for stopping cancer development, it is also how wounds initially repair themselves. However, if the immune system does not eliminate the senescent cells initially formed during the first steps of the wound repair process, then any further healing of the damaged tissue becomes compromised, SASP develops in the wound, and scar tissue begins to develop in that area [24]. With enough fibrosis, the

organ function becomes compromised. Examples of diseases characterized by fibrosis include atherosclerotic lesions in heart disease, COPD, liver and kidney failure, neurological lesions such as Alzheimer's, development of diabetes by loss of beta-cell function, and even obesity (as scar tissue can also form in the adipose tissue). More than 45% of all mortality is associated with significant fibrosis [25].

A primary cause of the inability of the immune system to remove senescence cells is chronic unresolved inflammation at cellular level [26]. This ongoing inflammation creates molecular background noise that disrupts the intricate recognition system of the immune system to eliminate senescent cells leading to the acceleration of a chronic disease. Furthermore, excess unresolved inflammation also makes it difficult for internal stem cells to replace the damaged cells to maintain normal organ function [27].

9. CONTROLLING IMMUNOLOGICAL RESPONSES

The Resolution Response also acts as the linkage between the innate and adaptive immune systems in the body. The innate immune system is hard-wired to rapidly respond to microbial invasions, but it has no retained memory of those pathogens. The adaptive immune system is much slower to react to microbial invasions, but retains a memory of past infections in order to generate a more elegant immunological defenses, especially in terms of antibody formation. Even for the adaptive immune system, the Resolution Response plays a key role due to the role of AMPK in the presentation of antigens [28, 29].

Therefore, if the Resolution Response is blocked, the initiation of inflammation by the innate immune system will not be totally resolved and there will be continued tissue damage below the perception of pain. In addition, without an optimal Resolution Response, the more sophisticated adaptive immune system will not be primed to produce more advanced immunological weapons, such as antibodies to generate protection against future microbial attacks.

10. THE ROLE OF NF-κB IN THE RESOLUTION RESPONSE

NF-κB is the gene transcription factor responsible for much of the body's initiation inflammatory response to any injury [7,30]. Thus, NF-κB can be viewed as the master switch for inflammation. In particular, once activated by external signaling, it causes the increased expression of the COX-2 enzyme responsible for the generation of eicosanoids as well as a large number of inflammatory cytokines, including TNFα, IL-1, and IL-6. While these inflammatory mediators are required to activate the innate immune system, the over-production of these inflammatory compounds makes it more difficult to completely turn off the initial inflammatory response caused by an injury. Rather than inhibiting this gene transcription factor by a drug, a more appropriate approach would be to modulate its activity by the diet. This can be done by reducing its activation via toll-like receptors (especially TLR-4) or RAGE (Receptor of Advanced Glycosylated End products), The reduction of TLR-4 activation of NF-κB can be achieved either by reducing the levels of metabolic endotoxemia induced by LPS fragments from gram-negative bacteria entering into the bloodstream, by increasing the integrity of the mucosal wall of the intestine, or by reducing the dietary consumption of TLR-4 mimetics, such as palmitic acid that can interact with the TLR-4 receptor. Likewise, the reduction of glycosylated proteins by reducing the dietary intake of glucose will reduce the potential activation of RAGE [31, 32]. Finally, reducing the cellular levels of the omega-6 fatty acid, arachidonic acid (AA), will reduce the levels of pro-inflammatory eicosanoids generated upon activation of the inducible COX-2 enzyme by NF-κB.

There is no direct marker of NF-κB activity. However, increased levels of cytokines in the plasma can be used an indirect marker of its increased activity within the cell.

11. THE ROLE OF EICOSANOIDS IN THE RESOLUTION RESPONSE

Once eicosanoids are formed, they become the foot soldiers to extend the initial inflammatory surge caused by an injury [33]. These hormones also have autocrine, paracrine, and exocrine properties that allow them to intensify the inflammatory response, while also affecting a number of other organs and thus, continuing the inflammatory response. The eicosanoids derived from arachidonic acid (AA) are 100-1,000 times more pro-inflammatory than the eicosanoids derived from the omega-3 fatty acid, eicosapentaenoic acid

(EPA). Thus, the AA/EPA ratio in the blood can be a surrogate marker of the ratio of AA and EPA in various organs. As the AA/EPA ratio increases in the blood, so will the levels of more inflammatory cytokines generated as a consequence of NF-κB activation. As a result, the intensity of the overall initial inflammatory response also increases. It should be noted that unlike the other primary omega-3 fatty acids, docosahexaenoic acid (DHA) does not form eicosanoids, but can be a precursor to form several critically important resolvins.

12. THE ROLE OF RESOLVINS IN THE RESOLUTION RESPONSE

Resolvins are a broad group of hormones derived from omega-3 fatty acids (primarily EPA and DHA) that are also classified as Specialized Pro-Resolving Mediators [34]. These hormones are essential in resolving the initial inflammatory response driven by eicosanoids and cytokines. They are also critical in stopping the swarming of neutrophils to an injury site as well as changing the phenotype of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype [35].

It usually requires high levels of supplemental EPA and DHA (greater than 3.4 grams per day) to observe changes in the steady-state levels of resolvins in the blood [36]. The higher the AA/EPA ratio in the blood, the more resolvins must be produced to eliminate the initial inflammatory signals caused by an injury.

13. THE ROLE OF AMPK IN THE RESOLUTION RESPONSE

AMPK is the final and most critical step of the Resolution Response. Although AMPK is not considered a classic gene transcription factor *per se*, it is an energy and glucose sensor that controls the phosphorylation of a number of other gene transcription factors that, in turn, regulate metabolism [13,14]. Thus, AMPK can be considered a master metabolic switch necessary for the rebuilding of damaged tissue as well as inhibiting NF-κB activity [12, 37, 38].

Similar to NF-κB, there is no direct blood marker of the increased activity of AMPK. However, an indirect marker of its activation would be a reduction of blood glucose levels as measured by HbA1c.

14. DIETARY CONTROL OF THE RESOLUTION RESPONSE

The molecular components of the Resolution Response discussed above are under significant dietary control that can either optimize or inhibit its ability to control healing. This is because each dietary component of the Resolution Response, described below, interacts with the highly conserved genetic and hormonal mechanisms discussed in the previous section that compromise the Resolution Response.

Therefore, the overall diet and specifically a personalized anti-inflammatory, calorie-restricted, protein-adequate, carbohydrate-moderate (but rich in fermentable fiber), low-fat (especially low in saturated and omega-6 fats) diet becomes an initial starting point for optimizing the Resolution Response. Since injuries are at random, maintaining such a diet on a continuous basis is essential for an optimal Resolution Response that is ready to respond immediately.

Such a diet was developed in the early 1990s to reduce diet-induced inflammation. The common name for this diet is the Zone diet [39]. The Zone diet has been demonstrated to be superior in the reduction of inflammation as measured by C-reactive protein compared to a placebo diet with an equal level of calorie-restriction, resulting in equal weight loss [40, 41].

The Zone diet was designed to modulate excess eicosanoid formation caused by insulin resistance in order to *reduce* inflammation [39, 42, 43]. Hence, the Zone diet is considered to be the best as an anti-inflammatory diet [44]. The hormonal responses induced by the Zone diet are short-lived (4-5 hours), so their orchestration to reduce inflammation requires consistent application of this approach [45]. The Zone diet is a calorie-restricted diet as it is protein-adequate and moderate in carbohydrates and can be used indefinitel,y as demonstrated in a five-year study with type 2 diabetic patients [46].

Even though inflammation can be reduced by following the Zone diet, the remaining residual inflammation has to be resolved by the hormones derived from omega-3 fatty acids. These are the resolvins. The final step of the Resolution Response is the repair of damaged tissue by the activation of AMPK that can be activated by dietary polyphenols. Thus, for Pro-Resolution Nutrition to

be successful, it requires the Zone diet to be continually used to reduce inflammation, and also provide adequate levels of omega-3 fatty acids to resolve the inflammation as well as adequate levels of polyphenols to repair the damage caused by inflammation.

The timing of these dietary-controlled events is sequential. This means the reduction of inflammation must take place before its final resolution can be completely achieved. Only after the injury-inflammation is resolved, can the repair of the damaged tissue be set in motion. All three steps are required to work together in a systems-based approach to optimize the Resolution Response. It should be noted that activation of AMPK by polyphenols also inhibits the activity of NF-kB, thus closing the loop of the Resolution Response to return the body back to homeostasis [12]. The successful result of this complex multi-step biological process, aided by following Pro-Resolution Nutrition, is what is commonly referred to as healing.

Following the Zone diet is easily accomplished by appropriate choices of readily available foods. On the other hand, consuming adequate levels of omega-3 fatty acids and polyphenols through a standard diet can be a challenging task due to their low concentrations in normally consumed food products (fish, fruits, and vegetables), thus for Pro-Resolution Nutrition to be a success may potentially require supplementation of concentrates of omega-3 fatty acid or extracts of polyphenols.

Omega-3 fatty acids are only found in high concentrations in fatty fish, such as sardines, anchovies, mackerel, and salmon. Sardines, anchovies, and mackerel have relatively high concentrations of polychlorinated biphenyl (PCBs), and most salmon is farm-raised using crude sardine and/or anchovy oil (also rich in PCBs) as a primary food additive necessary for their growth. As a result, the consumption of these natural sources that are rich in omega-3 fatty acids may result in higher PCB levels that can compromise the health benefits of the omega-3 fatty acids. Thus, having adequate sources of omega-3 fatty acids that are exceptionally low in PCBs, to produce adequate levels of resolvins, is a primary requirement for successful Pro-Resolution Nutrition. This potential problem can be accomplished by using highly purified omega-3 fatty acid concentrates.

Polyphenols are compounds that give fruits and vegetables their color. However, it is not the consumption of polyphenols *per se*, but their urinary levels that is strongly associated with slowing the development of chronic disease as well as decreased frailty and mortality and improved cognitive function [47-50]. The higher polyphenol levels in the urine are a direct consequence of their water-solubility ability to enter the blood. Unfortuantely, a majority of polyphenols do not meet this requirement. Furthermore, the concentration of polyphenols in vegetables and fruits is very low (about 1-2 percent by weight). As a consequence, most polyphenols are unlikely to enter the blood in high enough concentrates to activate AMPK. This is why the use of purified water-soluble polyphenol extracts provide a viable dietary solution to this problem. By using such purified extracts rich in water-soluble delphinidins (a subclass of anthocyanidins), it has been demonstrated that oxidative stress, as measured by urinary F2- isoprostanes, was significantly reduced at high levels of daily supplementation [51], and that levels of HbA1c in pre-diabetics are significantly reduced at slightly lower levels of daily supplementation [52].

If any one of the dietary modulators of Pro-Resolution Nutrition is not present in sufficient amounts to accomplish its assigned task, then the healing of any injury will be compromised. Furthermore, there must be a continuous orchestration and balance of each of these three unique dietary components of Pro-Resolution Nutrition to maintain an optimal Resolution Response to rapidly respond to random injury-induced inflammation. For example, the half-life of omega-3 fatty acids in the blood is approximately two days, compared to the half-life of polyphenols in the blood of approximately two hours. These half-lives are relatively long as compared to the total lifetime of hormonal changes generated by a meal, which is approximately five hours and suggests a half-life of approximately one hour. Thus, within a week of dietary non-compliance, many of the potential benefits of following Pro-Resolution Nutrition will be lost. In addition, it takes about three months to build up the ideal ranges, once one begins following Pro-Resolution Nutrition. Therefore, maintaining an optimal Resolution Response requires following Pro-Resolution Nutrition on a consistent basis.

15. ADDRESSING CELLULAR SENESCENCE

When optimized, the Resolution Response can potentially neutralize, if not eliminate, the inflammation induced by senescent cells, which is one of the long-term biological consequences of unresolved inflammation. Ideally, an optimal Resolution Response allows the immune system to eliminate senescent cells without toxicity, since it is diet-based. This approach is known as senolysis, as this stops the production of the SASP at its source. Thus, using Pro-Resolution Nutrition to optimize the Resolution Response could also be considered "senolytic nutrition". The result would be the slowing, halting, or even potentially reversing particular chronic diseases associated with aging as the levels of senescent cells are reduced. However, this non-pharmaceutical medical food approach requires a consistent and comprehensive nutritional intervention program that is personalized to the individual as determined by highly validated clinical parameters that can be determined using simple finger stick blood tests. These are described below.

16. PERSONALIZING PRO-RESOLUTION NUTRITION BY BLOOD TESTING

You cannot manage what you cannot measure. Medicine is no different. The key to the Pro-Resolution Nutrition program is its personalization, as determined by blood testing to optimize the Resolution Response of each patient. This personalization allows the adjustment of the protein-to-carbohydrate ratio of the Zone diet as well as determine the levels of any necessary supplementation with omega-3 fatty acid concentrates or polyphenol extracts to bring each blood marker into an ideal range.

As mentioned above, therapeutic doses of polyphenol extracts rich in delphinidins are effective in reducing oxidative stress and elevated blood glucose levels [51, 52]. Likewise, the use of therapeutic doses of omega-3 fatty acids have shown to have benefits in the treatment of severe brain trauma [53], age-related macular degeneration [54], and the regeneration of beta-cell function in type 1 diabetes [55-57]. All of these conditions can be linked to unresolved inflammation, ultimately caused by a blocked Resolution Response. The more that all three dietary components of Pro-Resolution Nutrition are used in a systems-based approach, the levels of any one particular dietary component can be correspondingly reduced.

The three blood markers, used to optimize the Resolution Response, are shown below:

1. *Triglyceride/HDL cholesterol (TG/HDL) ratio*: This is a surrogate marker of insulin resistance in the liver. This marker is reduced by following the Zone diet and primarily adjusted by changing the protein-to-carbohydrate ratio, while maintaining adequate protein intake.`
2. *Arachidonic acid (AA) to eicosapentaenoic acid (EPA) ratio*: This is a marker of the levels of unresolved inflammation as well as the levels of cytokines in the blood [58]. This marker is primarily reduced by an adequate intake of omega-3 fatty acids.
3. *Glycosylated hemoglobin (HbA1c):* This is a marker of long-term blood glucose control, which will indicate the degree of inhibition of AMPK as elevated blood glucose levels inhibit AMPK activity [59-61]. This marker is primarily reduced by adequate levels of polyphenols.

There is also significant cross-talk between the various dietary interventions of Pro-Resolution Nutrition and various blood markers. For instance, a calorie-restricted Zone diet and the resolvins generated from omega-3 fatty acids will have some effect on the activation of AMPK. Likewise, the omega-3 fatty acids and polyphenols will have some effect on reducing insulin resistance. Finally, the Zone diet was designed to lower AA levels, so it will have some effect on the AA/EPA ratio. The more all three dietary interventions are involved, the less reliance one needs to put on any one of the dietary interventions of Pro-Resolution Nutrition to optimize the Resolution Response.

The blood tests used are convenient and inexpensive because they are finger stick tests, they can be done by the individual at home, in a walk-in pharmacy, or in a physician's office. They are recommended every three months in the first year of the program, and then on an yearly basis thereafter, to ensure continuing compliance in optimizing the patient's internal Resolution Response.

The ranges of these simple tests that indicate whether or not the internal Resolution Response has been optimized are listed below in Table **1**.

Table 1. Summary of clinical markers.

Marker	Measures	Ideal Range
TG/HDL ratio	Insulin resistance in the liver	Less than 1
AA/EPA ratio	Balance of inflammation to resolution	1.5-3
HbA1c	Activation of AMPK	4.9-5.1%

Only when each of these markers is in their ideal ranges, can the patient's internal Resolution Response be considered to be optimized.

Following Pro-Resolution Nutrition, it is often possible to reach these guidelines within a matter of months. The key is to maintain those markers in their appropriate ranges as long as possible, by maintaining the efficacy of the Resolution Response not only for minimizing damage of random future injuries, but also to enhance the elimination of existing senescent cells and fibrosis by activation of the immune system.

CONCLUSION

The Resolution Response theory of chronic disease provides a new molecular definition of wellness as keeping inflammation in a *therapeutic zone*. This means having the body able to generate an appropriate level of the initial inflammatory response to an injury to curtail the potential tissue damage but then balanced by an equal ability to resolve the injury induced-inflammation and then repair the tissue damage caused by the initial inflammation.

The basic premise is that unresolved inflammation caused by a blocked Resolution Response may be a major factor in both the creation of senescent cells and the development of fibrosis that is associated with a wide number of chronic disease conditions. Furthermore, that same blocked Resolution Response may be a major underlying cause of the immune system's reduction of efficiency with aging (*i.e.*, immunosenescence). This decreased efficacy of the immune system prevents the normal removal of senescent cells, which leads to their persistence and accumulation causing the acceleration of a variety of chronic diseases and continued organ fibrosis. Finally, a blocked Resolution Response may disrupt the efficiency of the adaptive immune system to produce anti-antibodies necessary to respond to microbial infections.

There is no drug therapy that can realign the Resolution Response, but an appropriate dietary system can optimize it. If the initial investigations of the dietary control of the Resolution Response continue to hold promise, this could potentially usher in a new era of diet/pharmaceutical interactions to treat a wide variety of chronic disease conditions with a far greater therapeutic index resulting in a significantly increased health span.

LIST OF ABBREVIATIONS

AA = Arachidonic acid

AMPK = AMP-activated protein kinase

COX-2 = Cyclooxygenase-2

DHA = Docosahexaenoic Acid

EPA = Eicosapentaenoic Acid

NF-κB = Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells

RAGE = Receptor For Advanced Glycation End

SASP = Senescence-Associated Secretory Phenotype

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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