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Forum Review

The Molecular Inflammatory Process in Aging

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ABSTRACT

Emerging pathological evidence indicates that major chronic aging-related diseases such as atherosclerosis, arthritis, dementia, osteoporosis, and cardiovascular diseases, are inflammation-related. In this review, inflammation is examined as a possible underlying basis for the molecular alterations that link aging and age-related pathological processes. A proposal for the molecular inflammation hypothesis of the aging views the redox derangement that occurs during aging as the major factor for increased risk for age-related inflammation. Accumulated data strongly indicate the activation of redox-sensitive transcription factors and dysregulated gene expression under the age-related oxidative stress seems to be the major culprits. Key players involved in the inflammatory process are the age-related upregulation of NF-κB, IL-1β, IL-6, TNFα, cyclooxygenase-2, adhesion molecules, and inducible NO synthase. Furthermore, data are presented on the molecular events involved in age-related NF-κB activation and phosphorylation by IκB kinase/NIK and MAPKs. Experimental data on antiaging calorie restriction (CR) for its antiinflammatory efficacy by suppressing the upregulated proinflammatory mediators will be reviewed. Also, the involvement of another super family of transcription factors, PPARs (PPARα, γ) as regulators of proinflammatory responses and NF-κB signaling pathway is described as well as a discussion on the physiological significance of a well-maintained balance between NF-κB and PPARs. *Antioxid. Redox Signal.* 8, 572–581.

INTRODUCTION

A MAJOR CHARACTERISTIC of the aging process is functional deterioration with time, accompanied by increased vulnerability to diseases. Although the underlying cause of aging is unknown, the currently popular oxidative stress hypothesis of aging provides molecular insights into possible causative factors for aging (92, 93). According to tenets of this hypothesis, the combined effect of accumulated oxidative damage and weakened antioxidative defense systems causes a disturbance in the organism's redox balance, which leads to aging and age-related degenerative diseases (17, 31, 43, 93). One of the most intriguing and important questions is, how does a disrupted redox balance increase vulnerability to disease during aging. As will be described in the following sections, we believe the answer might lie with the activation of redox-sensitive transcription factors that cause the inflammation process.

Major culprits of the redox imbalance that occurs from age-related oxidative stress are likely increased reactive species (RS), such as oxygen-derived reactive species (ROS), nitrogen-derived reactive species (RNS), and reactive lipid aldehydes, coupled with a weakened antioxidant defense capacity. To ensure a properly maintained redox balance, organisms require an intricate, well-coordinated network of antioxidants from various sources that control these RS as well as a functioning, overall defense system.

Emerging evidence from molecular work on oxidative stress-induced redox imbalance shows that the activation of many of redox-sensitive transcription factors causes the generation of various proinflammatory molecules (56). It is noteworthy that these activated proinflammatory genes are com-

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monly observed during aging (8, 17). Based on what is known about inflammation as the underlying process of many age-related, chronic diseases and an organism's increased susceptibility to various inflammatory stimuli, including oxidative stress, we proposed "the molecular inflammation hypothesis of aging" to provide a molecular basis for the link between normal aging and pathological aging processes (18, 19). To highlight the importance of underlying subtle molecular alterations at the gene level, rather than gross inflammatory lesions, we selected to use the term, "molecular inflammation." Implicated in this hypothesis is the notion that the molecular activation of proinflammatory genes by altered redox-sensitive cellular signal pathways would eventually lead to fully expressed inflammatory tissues and organs, which is exacerbated by the progression of time (i.e., aging) (17–19). Inflammation is already linked with dementia (63) cardiovascular disorders (83), arthritis (5), cancers (12), and other disorders (76). Recent data on healthy centenarians showing low levels of inflammatory biomarkers are consistent with the basic tenet of the molecular inflammation hypothesis (28).

Based on what was learned from research on calorie restriction (CR) in its ability to regulate proinflammatory gene expressions and its antiaging action, we constructed a schema depicting the molecular inflammatory process during aging (Fig. 1) as a possible bridge between normal aging and age-associated disease processes.

In this review, we attempt to summarize the molecular evidence on the age-dependent proinflammatory process by examining various oxidatively altered redox-sensitive transcription factors and the modulated signal pathways. Our review will begin with some of the major players involved in the inflammation process: cyclooxygenase (COX), nitric oxide synthase (NOS), and redox-sensitive transcription factors, such as nuclear factor κB (NF-κB) and peroxisome proliferator-activated receptors (PPARs). Then, using the vascular aging process as a model, we highlight the molecular modulation of these major mediators by CR, which is known to have potent antioxidative and anti-inflammatory actions (18, 19, 93).

PROINFLAMMATORY COX-2 AND INDUCIBLE NOS (iNOS)

Changes of COX-2 in aging

COX, a key enzyme involved in prostaglandin (PG) synthetic pathways, converts arachidonic acid to PGH_2, during which time ROS are generated (6). This ROS production in the PG synthesis pathway can contribute significantly to the overall ROS pool under normal and pathogenic conditions, but particularly during aging (11).

Although the role of COX in PG synthesis is well known, increased production of PG in aged animals has not been well explored (22, 87). For example, macrophages from old mice are reported to produce more proinflammatory PGE_2 than young mice, providing some basis for age-related increases in the proinflammatory process (87). Existing data also indicate elevated production of several proinflammatory PGs during aging, while showing decreased cytoprotective PGI_2 with advancing age (65).

The extent of COX-derived ROS during aging in rats has been reported from experiments utilizing the COX-specific inhibitor, indomethacin (20, 49). Results show a steady increase of PG-dependent ROS generation with age, and at 24 months, a significant increase (87% higher than the 6-month-old rats) was noted (49). Moreover, mRNA expression of COX-2 is shown to increase with age (20, 49, 88), which sets a conducive condition for age-associated inflammatory activation.

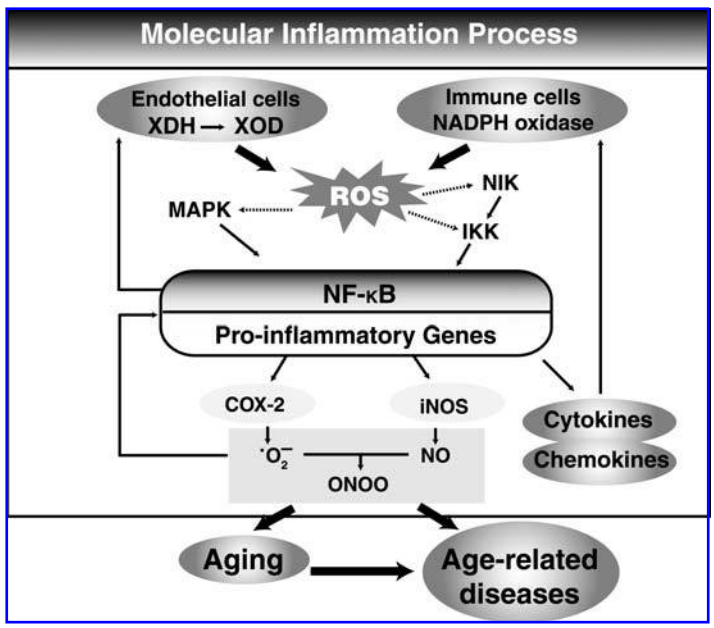

FIG. 1. A schematic illustration of the effects of oxidative stress on the activation of molecular inflammation during aging. Generation of ROS by XOD and NADPH oxidase stimulates MAPK and NIK/IKK pathway, activates upstream signal pathway of NF-κB, or activates NF-κB directly. Upregulation of NF-κB leads to the expression of inflammatory mediators, COX-2, iNOS, cytokines, and chemokines, which produces reactive species such as $\cdot O_2^-$, NO, and $ONOO^-$. Accumulation of reactive species causes aging and age-related diseases. *See* Abbreviations for list of definitions.

iNOS in aging

Nitric oxide (NO) is one of the most physiologically important radical species essential to proper vascular function (64). NO is synthesized enzymatically from L-arginine by NOS. Constitutive and inducible isoforms of NOS have been characterized and differentiated by their dependence on Ca^{++}/calmodulin. The expression of inducible NOS (iNOS) occurs in many cell types including macrophage, epithelial, and chondrocyte, in response to inflammatory and immunological stimuli such as cytokines (81). Excessive production of NO by iNOS causes the pathogenesis and destruction of various tissues as seen in chronic inflammatory processes, including those attributed to vascular diseases, diabetes, arthritis, dementia, sepsis, multiple sclerosis, and irritable bowel syndrome (73, 94).

The findings showing that the inflammation process is accompanied by the production of large amounts of NO strongly implicate iNOS a major player in chronic inflammatory diseases. Cernandas *et al*. (13) reported that the expression of iNOS is enhanced in vessel walls of aged rats. In a later work with Fischer 344 rats, our laboratory also found increased iNOS gene expression in kidney with age (45).

From the standpoint of the inflammation process, NO is a strong contributor to the inflammation process as its enhanced unregulated activity causes increased vascular permeability (60). Much of the known involvement of NO in inflammatory responses relates to its ability to form a nonradical, but potent oxidant, peroxynitrite ($ONOO^-$) (78). During inflammatory responses, a series of events lead to the activation of residential macrophages and the recruitment of leukocytes from the circulatory system to the injured sites, inducing $ONOO^-$ production (57). $ONOO^-$ inhibits function of mitochondrial respiratory chain enzymes, oxidizes various proteins, and possibly triggers DNA strand breakage (69). Nitrated proteins by $ONOO^-$ have been widely detected in chronic inflammation, atherosclerotic lesions, coronary arteries, ischemia-reperfusion, shock, and cancer (57, 74).

REDOX-SENSITIVE NF-κB IN INFLAMMATION AND AGING

NF-κB was first described as a B-cell-specific factor that binds to a short DNA sequence motif located in the immunoglobulin κ light chain enhancer; however, NF-κB is now known to be expressed in all cell types and plays a central role in regulating gene transcription (72). Activations of NF-κB and its targeting genes are associated with various pathological processes (2). Recent investigations on the regulation of NF-κB focused on the phosphorylation of inhibitor of NF-κBs (IκBs). So far, two closely related kinases, IκB kinase α (IKKα) and IKKβ, have been identified as key players in NF-κB modulation (95); the IKKα/IKKβ heterodimer is associated with the regulatory subunit, IKKγ (46). In response to various stimuli, upstream kinases are activated and recruited to the complex via IKKγ, resulting in the phosphorylation of IKKβ (i.e., activation of IKK). The activated IKK complexes phosphorylate IκB subunits of NF-κB/IκB to trigger the degradation of IκB, leading to the activation of NF-κB (4, 46, 95).

NF-κB is among the most important transcription factors shown to respond directly to oxidative stress conditions (34). Reactive oxygen species enhance the signal transduction pathways for NF-κB activation in the cytoplasm and translocation into the nucleus (44). Because of its sensitivity to the oxidative status, the regulation of NF-κB is greatly influenced by the intracellular redox status and plays a major role in the regulation of inflammation processes during aging (39, 52). Among proinflammatory genes that encode proteins for orchestrating inflammatory responses, many signaling proteins such as cytokines, growth factors, or chemokines are regulated by NF-κB (2, 72). Under normal physiological conditions, NF-κB activation in response to proinflammatory signals is short-lived, and the reaction stops quickly once the signal is terminated. However, if the activation signal persists, as in the aging process, a chronic inflammatory condition would have far reaching effects. Interestingly, some of the NF-κB-induced proteins are known to act as potent NF-κB activators, creating an auto-activating loop (36), and consequently more synthesis of inflammatory mediators.

Consistent findings show evidence that DNA binding activity and transcriptional activity of NF-κB are enhanced in old rodents, as found in heart, liver, kidney, and brain tissues (38, 50). Further several studies report that the upregulation of NF-κB activity is accompanied by increased ROS production during aging (49). These results provide strong experimental evidence that increased NF-κB activity in aged animals is likely due to the increased intracellular oxidative status during aging. Evidence is clear now that increased NF-κB activity during aging is elicited through the phosphorylation of IκB kinase to cause the degradation of IκBα and IκBβ (50). These findings along with data from other investigations provide support for the molecular inflammation process as a bridge between normal and pathological aging processes (48, 55).

IMPLICATION OF PPARS IN INFLAMMATION AND AGING

PPARs are transcription factors belonging to the nuclear hormone receptor superfamily. At present, three different isotypes of PPARs (α, β/δ, and γ) with distinct tissue distributions and functions are characterized (53). PPARs play major roles in a broad spectrum of biological processes, including cell proliferation and differentiation, glucose homeostasis, eicosanoid signaling, insulin sensitivity, glucose and lipid metabolism, bone formation, and tissue remodeling (32, 52, 84). PPARs are activated by endogenous fatty acids and their derivatives, subsequently forming heterodimers with another nuclear receptor, retinoid X receptor (RXR), and binding to specific peroxisome proliferator response elements (PPRE) present within the promoter regions of target genes (53).

More relevant to the main topic of this review on inflammation, PPARα and PPARγ have been implicated as regulators of inflammatory responses (14, 30, 42, 70). Recent molecular studies show that the induction of oxidative stress downregulates PPARs (3, 62). Also, several studies have demonstrated that PPARα and PPARγ inhibit the expression of

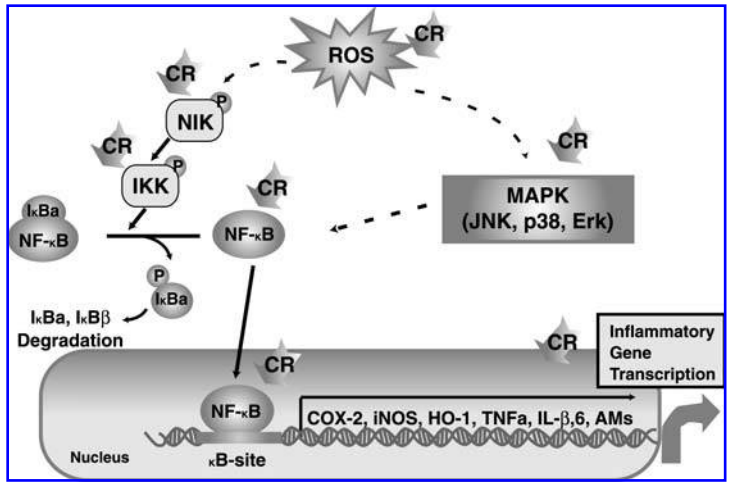

FIG. 2. Suppression of NF-κB activation by CR. NF-κB is sequestered in the cytoplasm by NF-κB inhibitory proteins (IκBs). Stimulation by ROS leads to the activation of signaling cascades NIK/IKK and MAPK pathway. Activated NF-κB by NIK/IKK and MAPK pathways, which is then translocated to the nucleus, where it binds to κB elements and activates the transcription of various genes involved in inflammatory and immune responses. *See* Abbreviations for list of definitions.

inflammatory genes, such as cytokines, metalloproteases, and acute phase proteins (14, 42, 70). Interestingly, all available data indicate that activation of PPARs modulates oxidative stress-sensitive pathways, redox-responsive nuclear NF-κB, activator protein-1 (AP-1), and signal transducers and activators of transcription (STAT) (7, 24). These findings strongly indicate an important role for PPARs in controlling the inflammatory process, which could be potential therapeutic target sites for age-related inflammatory diseases, as shown in a study with the supplementation of PPARα agonist, Wy 14,643 and dehydroepiandrosterone sulfate (DHEAS) that suppressed the age-induced upregulation of NF-κB activity and the expression of several NF-κB-regulated genes (68).

Interestingly, PPARα-deficient mice are shown to have higher levels of oxidative stress at an earlier age than wild-type mice and have an exacerbated inflammatory response to lipopolysaccharide (LPS) stimulation (24). As reported by Deplanque *et al.*, the activation of PPARα exhibits a neuroprotective effect via the mechanism to decrease cerebral oxidative stress, depending on the increase of numerous antioxidant enzyme activities (26). Another recent paper reported that the activation of PPARα induces mRNA and protein expression of IκBα and reduces NF-κB DNA binding activity (25). All of these results show a strong implication of PPARα's involvement in the oxidative stress and inflammation processes.

PPARγ activation by its agonists may interrupt the NF-κB and AP-1 pathways, downregulating NF-κB and AP-1-dependent gene activation, including COX-2, iNOS, and cytokines. Chung *et al.* (21) recently reported that PPARγ inhibits NF-κB-driven transcription by directly interacting with both p65 and p50. In addition, the activation of PPARγ is shown to reduce oxidative stress and nitrative stress (80), which may play a significant role in attenuating the age-related redox disturbance.

Recently Sung *et al.* (77) reported a decrease in mRNA level, nuclear protein levels, and DNA binding activity of PPARs with age. Considering the essential roles of NF-κB and PPARs in the molecular modulation of a wide variety of cellular processes, the balance between NF-κB and PPARs may have a great impact on the metabolic status of an organism in relation to inflammation, as highlighted in an interesting review by Chinetti *et al.* (16).

ROLE OF CR IN MODULATING MOLECULAR INFLAMMATION AND AGING

CR remains the only known robust means of extending lifespan and delaying age-related physiological changes and the onset of a wide range of age-related diseases in rodents (37, 61, 85, 91, 93). The enhanced metabolic efficiency that CR produces and its ability to increase stress resistance over the lifespan have been hypothesized as the core of CR's anti-aging effects (37, 61, 85, 91). The antiinflammatory action of CR has been reported by several studies (8, 18), and two publications on gene expression profiling of aging rodents have shown that stress-related and proinflammatory genes are selectively suppressed by CR, further strengthening the argument for the antiinflammatory action of CR (11, 58).

Evidence showing antiinflammatory action by CR in the suppression of COX-derived ROS generation in the presence of indomethacin is noteworthy (20, 49). It was shown that CR suppressed COX-derived ROS generation from a level of 26.36% in *ad libitum*-fed rats to 16.55% in the CR group, concomitantly blunting COX activity and thromboxane A_2 (TXA_2) production (20). These findings provide additional evidence on what is known about the antiinflammatory and anti-oxidative actions of CR at the molecular level.

The beneficial effects of CR can be further extended to its ability to regulate gene expression as evidenced by the modulation of COX-2 mRNA and protein levels through NF-κB manipulation (1, 49). Many other proinflammatory mediators are similarly modulated by CR, such as, interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor α (TNFα), and iNOS (56), as summarized in Table 1. Because most of these genes are under the control of NF-κB, the ability of CR to regulate NF-κB might be the pathway by which CR exerts its attenuating effects on those genes. Data clearly show the ability of CR to suppress age-dependent increases in NF-κB

Table. 1. Changes in Inflammation-Related Factors

		Inflammatory process	*Aging process*	*CR*	*PPAR activators*
Redox state	Reactive oxygen species	↑	↑	⊢	⊢
	Reactive nitrogen species	↑	↑	⊢	⊢
	Catalase, Superoxide dismutase	↓	↓	⊢	⊢
	GSH peroxidase, GSH/GSSG	↓	↓	⊢	⊢
Proinflammatory enzymes	Inducible NO synthase	↑	↑	⊢	⊢
	Heme oxygenase-1	↑	↑	⊢	⊢
	Cyclooxygenase-2	↑	↑	⊢	⊢
	Conversion of xanthine dehydrogenase to xanthine oxidase	↑	↑	⊢	⊢
Proinflammatory cytokines	IL-1β	↑	↑	⊢	⊢
	IL-6	↑	↑	⊢	⊢
	TNFα	↑	↑	⊢	⊢
NF-κB activation	NF-κB DNA binding activity	↑	↑	⊢	⊢
	NIK/IKK activation	↑	↑	⊢	⊢
	Phosphorylation of IκBα	↑	↑	⊢	⊢
	Degradation of IκBα and IκBβ in cytoplasm	↑	↑	⊢	⊢
	Nuclear translocation of p65 and p50	↑	↑	⊢	⊢
	NF-κB-dependent gene expression	↑	↑	⊢	⊢
	Active MAPKs (ERK, JNK, p38 MAPK)	↑	↑	⊢	⊢
Adhesion molecules	E-selectin	↑	↑	⊢	⊢
	P-selectin	↑	↑	⊢	⊢
	VCAM-1	↑	↑	⊢	⊢
	ICAM-1	↑	↑	⊢	⊢
Hypoxic markers	HIF-1α	↑	↑	⊢	NK
	VEGF	↑	↑	⊢	NK
	EPO	↑	↑	⊢	NK

↑, increased; ↓, decreased; ⊢, blunted; NK, not known.

through the upregulation of cytoplasmic IκBα and IκBβ by inhibiting IKK activity (48, 55). More recently, we found that CR blunted the reduction of expression and activation of PPARs during aging (77). The inhibitory role of PPARs in NF-κB activation through CR provides strong evidence for CR's underlying antiaging action via its antiinflammatory effects.

Another important transduction pathway that is altered during aging counteracted by CR is mitogen-activated protein kinases (MAPK) signaling (47). All eukaryotic cells carry out signal transduction through multiple MAPK pathways in response to various stimuli, including oxidative stress (86). Three subtypes of MAPKs are identified: extracellular signal regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK. The importance of the involvement of MAPK family members in the regulation of various cellular inflammatory responses has been increasingly appreciated. For instance, TNFα can induce a rapid and transient activation of ERK, JNK, and p38 MAPK (79), which in turn controls the transcription and synthesis of TNFα (40).

Available evidence also implicates the involvement of aberrant MAPK activation in various oxidative stress-related conditions (33, 41, 66, 89). For instance, Xhu *et al.* reported that JNK is activated and redistributed in the degenerating neurons of Alzheimer's disease (AD) (89). Gupta *et al.* reported that increased ROS levels contribute to MAPK activity in a malignantly progressed mouse keratinocyte cell line (33). Peters *et al.* suggested the involvement of MAPK activation in ROS-induced endothelial dysfunction and decreased contractile function in isolated rat thoracic aorta (66).

MAPK activity is now well documented to increase under the influence of aging, and to be modified by CR through its antioxidative and antiinflammatory actions (47). Peters *et al.* found the age-related activation of MAPK with a corresponding increase in ROS was consistently downregulated by CR at all ages studied (66). It should be noted that the chronic activation of MAPK seen in the chronic inflammation of old animals likely leads to age-dependent functional alterations (86). The attenuation of stress-activated MAPKs by CR may well be related to the calorie-restricted organism's enhanced mechanism for controlling the inflammatory process.

MOLECULAR INFLAMMATION AND VASCULAR AGING

Many gerontologists share the view that vascular aging may be the major underlying factor influencing the overall aging process in the whole body (90). This view is readily understandable by the fact that the blood vessel is solely responsible for the adequate supply of nutrients and oxygen to all individual cells, and any interruption causing less optimum blood circulation would cause a profound impact on cellular activities, consequently causing functional damages.

Proinflammatory changes in vasculatures

Age-associated changes in blood vessel structures are characterized by increased vascular intimal thickness and vascular stiffness, both of which may result from age-related pro-inflammatory status. For instance, one cause of vascular intimal thickness is the migration and matrix production of vascular smooth muscle cells (SMC) (75). It has been reported that enhanced arterial angiotensin II (Ang II) with age-induced monocyte chemoattractant protein-1 (MCP-1) expression stimulates SMC migration in the old (82). Growing evidence indicates that Ang II induces its pleiotropic vascular effects through NADPH-driven ROS generation (15). Chen *et al.* reported Ang II induces inflammation and end organ injury through its activation of the pro-inflammatory transcription factor, NF-κB (15). In addition, MCP-1 is a key molecule for monocyte chemotaxis and tissue extravasations and for the modulation of leukocyte function during inflammation (67), in particular, having a central role in restenosis and atherogenesis (27). These findings clearly revealed the participation of the molecular inflammatory process in vascular aging.

Vascular intimal thickness is also increased by changes in matrix proteins, which are suspected to be due to age-associated over-expression and/or dysfunction in extracellular matrix-degrading enzymes, such as matrix metalloproteinases (MMPs). However, synthesis and activation of MMP-2 may be mediated by the stimulation of local inflammatory cytokines (29). Li *et al.* (59) reported that basal production of MMP-2 in SMC does not differ significantly with aging, but that enhanced MMP-2 levels were observed in old versus young vascular SMC after stimulation by cytokines, including IL-1β, TNFα, and tumor growth factor-1β (TGF-1β). These data suggest that enhanced MMP-2 levels in the thickened intima of aortas in aged rats may reflect a chronically enhanced level of cytokine stimuli *in vivo* (10).

Endothelial cells as inflammatory sites

Functional changes in blood vessels during aging may be greatly influenced by alterations in vascular endothelial cells (EC). This is because ECs act as a blood vessel barrier and is a major regulator of blood vessel tone. Because of their localization in the vessel walls, the exposure of ECs to incessant external stresses, such as oxidized lipids and proteins in the plasma, can exacerbate endogenous oxidative stress in ECs.

One of the most important signs of endothelial cell dysfunction during aging is the increased expression of adhesion molecules (AMs) (96). AMs are transmembrane proteins responsible for cell-cell/cell-matrix interactions. Under normal physiological conditions, AMs are maintained in low concentrations; however, their expression is significantly induced by signals related to inflammation, which trigger an inflammatory response and recruit immune cells into the vessel wall. We recently reported that soluble AMs levels in serum that were used as inflammatory markers were elevated by the aging process (96). In rat aorta, we also found the expression of the major EC AMs (VCAM-1, ICAM-1, E-selectin and P-selectin) was upregulated with age due to enhanced oxidative stress during aging (97). The upregulation of AMs may be responsible for several vascular diseases that manifest with age. These new findings strongly indicate the inflammatory process is taking place in the aged aorta.

Other physiologic inflammatory mediators, such as cytokines, send signals to initiate various inflammatory responses, also change with aging and influence EC functions (90). Our laboratory found enhanced expression of pro-inflammatory cytokines, IL-1β, IL-6, TNFα, and MCP-1 in aorta tissue with age (97). The aging process may also change responses of ECs to cytokines and cytokine networks in ECs. Coe *et al.* reported that when endothelial cell cultures were generated from cerebral blood vessels, those derived from aged donors produced significantly more IL-6 in response to IL-1β, LPS, and hypoxia (23). The upregulation of these cytokines would act in both autocrine and paracrine ways to induce further inflammatory responses in the vasculatures (35), as shown in the overexpression of adhesion molecules and the activation of the transcription factor, NF-κB.

Effects of CR on pro-inflammatory aged vasculature

An association between inflammation and vascular aging can be found when observing CR action on age-related vascular alterations (51, 90, 96). CR is consistently shown to attenuate almost all age-related vascular modifications (96). Our laboratory found that CR can block aging-associated RS production and inflammatory PGs generation (51). Suppressed expressions of pro-inflammatory genes by CR include iNOS (45); PG synthesis enzymes cytosolic phospholipase A_2 (PLA_2) and COX-2 (51); adhesion molecules E-/P-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) (96, 97); pro-inflammatory cytokines IL-1β, TNFα, IL-6 (50); and inducible protein-10 (IP-10); and pro-apoptosis p21 and p53 (unpublished data). The potent antioxidant capacity of CR can be partly related to its efficiency on the antioxidative defense system, including the first line antioxidants GSH, vitamins C and E, urate, and antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). For instance, data show that CR maintains reduced thiol levels in the aged aorta, thereby protecting the vasculature from oxidative damage (51, 96). In addition, CR was found to boost the gene expression of the major antioxidant enzyme, vascular catalase (51).

LPS is a widely used inducer of inflammation, and its administration to experimental animals exacerbates the severity of the age-related proinflammatory state (9). We found that aging-induced expression of aortic AMs and level of soluble AMs were further elevated by the LPS-challenge (96). This finding implicates LPS to exacerbate the existing oxidative stress in the old animals and to further induce the generation of pro-inflammatory AMs.

CONCLUSIONS

Inflammation is a primary defense against threats to homeostasis. With aging, inflammatory responses may be overreactive or even cause damage, resulting in adverse pathological conditions. The proposed molecular inflamma-

tion hypothesis attempts to formulate a molecular basis for changes from a normal inflammatory process to age-related pathological processes during aging. In this review, we described the aging effects of several key players in age-related inflammatory reactions. An emphasis was given to NF-κB because it occupies a central position in the inflammatory process that influences various redox-responsive phosphorylations by NIK/IKK. We also reviewed the emerging evidence of relationships between PPARs and inflammation and the antiinflammatory actions of CR. Implications of PPARs as important mediators in the inflammatory process are particularly interesting because the possible link between insulin resistance and inflammation is of significance (71). Thus, the accumulating evidence on inflammation-related chronic diseases highlights the important role of molecular inflammation as a possible prime factor underlying many age-related diseases and provides a better understanding in terms of both basic biology and clinical application. In addition, recent revelations on the role of adipocyte-derived cytokines, such as leptin, and adiponectin, in vascular endothelial cells should give rise to more innovative ways to treat vascular aging (54). In summary, future therapeutic interventions should be based on multi-factorial strategies because of the extremely diverse nature of the inflammatory process, which should go beyond the inhibition of COX-2.

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ABBREVIATIONS

AD, Alzheimer's disease; AM, adhesion molecule; Ang II, angiotensin II; AP-1, activator protein-1; CAT, catalase; COX, cyclooxygenase; CR, calorie restriction; DHEAS, dehydroepiandrosterone sulfate; EC, endothelial cells; ERK, extracellular signal regulated kinase; GPx, glutathione peroxidase; IκB, inhibitor of NF-κB; ICAM-1, intercellular adhesion molecule-1; IKK, IκB kinase; IL-6, interleukin-6; IL-Iβ, interleukin-1β; IP-10, inducible protein-10; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; NF-κB, nuclear factor κB; NIK, NF-κB-inducing kinase; NO, nitric oxide; NOS, nitric oxide synthase; $ONOO^-$, peroxynitrite; PG, prostaglandin; PLA_2, phospholipase A_2; PPAR, peroxisome proliferator activated receptor; PPRE, peroxisome proliferator response elements; RNS, nitrogen-derived reactive species; ROS, oxygen-derived reactive species; RS, reactive species; RXR, retinoid X receptor; SMC, smooth muscle cell; SOD, superoxide dismutase; STAT, signal transducers and activators of transcription; TNFα, tumor necrosis factor α; TXA_2, thromboxane A_2; VCAM-1, vascular cell adhesion molecule-1.

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