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Growing old with nuclear factor–κB

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Abstract The transcription factor nuclear factor–κB (NF-κB) is involved in the regulation of a broad spectrum of genes that play important roles in a myriad of physiological and pathological events ranging from the immune response to carcinogenesis. Interestingly, many processes in which NF-κB plays a central role have long been noted for their alteration with age. A number of research groups have reported rather dramatic changes in NF-κB activity as humans and animals age, with tissue-specific increases and decreases in NF-κB activity being reported. The extent to which changes in NF-κB activity drive aging and influence life span in humans and other mammals is not clear. However, given the dramatic impact that NF-κB can have on the function of numerous tissues and organs, understanding how NF-κB activity changes with age will undoubtedly enhance our understanding of the many diseases associated with growing old.

NF-κB AND CELL DEATH

Before discussing the association of NF-κB and aging, it is instructive to consider its role in regulating programmed cell death. Although NF-κB activation is often associated with cell survival, many instances have been identified in which its activation promotes apoptosis. NF-κB is a homo- or heterodimer assembled from 5 potential subunits (RelA [p65], RelB, c-Rel, p50, and p52), and the different subunit combinations can have starkly different biological effects (Baldwin 1996, 2001a, b). Analysis of RelA knockout mice and cells expressing dominant negative forms of IκB-α (an NF-κB inhibitor) revealed a critical role for RelA-containing NF-κB complexes in protecting cells from tumor necrosis factor (TNF)-α–induced cell death (Beg and Baltimore 1996; Van Antwerp et al 1996). NF-κB was likewise found to protect cells from death induced by cancer chemotherapeutic agents (Wang et al 1996). However, equally compelling data show that NF-κB can sensitize cells to apoptosis induced by viral infection, and in some cases, to cell death triggered by the Fas receptor pathway (Lin et al 1995, 1998; Ivanov et al 1997; Matsui et al 1998; Chan et al 1999; Kasibhatla et al 1999). It is accepted by most researchers in the apoptosis field that NF-κB can promote cell survival or cell death, depending on the cell type and the death-inducing agent (Baldwin 2001a, b). As the role of NF-κB in aging is studied further, it is likely that a similar paradigm will emerge: alterations in NF-κB activity will be highly cell-type and stimulus dependent. Another concept from the cell death literature concerns the influence of the NF-κB subunit composition. For example, RelA is critical for maintaining hepatocyte viability during development, whereas other subunits are dispensable (Beg et al 1995). It seems likely that different subunits will respond to aging in distinct manners. As in the field of apoptosis, it will be critical in the aging field to fully characterize the subunit composition of NF-κB and to determine NF-κB activity not only in terms of deoxyribonucleic acid (DNA) binding but also in terms of its ability to activate transcription because transcriptional activation of NF-κB can also be regulated after DNA binding (Sizemore et al 1999; Madrid et al 2000, 2001).

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NF-κB AND THE AGING IMMUNE RESPONSE

Because NF-κB was originally discovered as a transcriptional activator involved in regulating immunoglobin production by B cells, it seems appropriate to first address how aging influences NF-κB activity in immune cells (Sen and Baltimore 1986a, 1986b; Singh et al 1986). It has long been recognized that advanced age is associated with a general decline in immune function and an increased susceptibility to bacterial and viral infection (Miller 1996). Dedicated work by numerous research groups has iden-

tified discrete steps in the immune response that diminish with age. The immune response can be separated into 2 distinct, but overlapping phases: the innate and acquired immune responses. The innate immune response involves the infiltration of infected tissues by neutrophils and macrophages that phagocytose invading microbes for destruction with granular proteases and superoxide radicals. Antigenic epitopes of the degraded microbes are then displayed in association with major histocompatibility complex (MHC) class II molecules for binding by appropriate T cells (CD4+). The binding of T cells to their antigens initiates the acquired phase of the immune response. As the acquired phase of the immune response progresses, antigen-activated T cells proliferate and produce critical cytokines, which in turn facilitate the differentiation of B cells into antigen-generating plasma cells. The acquired phase of the immune response also features the production of cytotoxic T cells, which induce apoptosis of cells displaying viral antigens in association with MHC class I molecules. Both the innate and acquired arms of the immune response are suppressed in older humans and animals (Lord et al 2001), and both phases prominently feature NF-κB as a critical regulator of cell activation.

Immunosenescence associated with age is characterized by a number of changes in the acquired immune response. T cell phenotypes shift from Th1 to Th2 as individuals age, which in turn alters the antibody isotypes generated by B cells. In addition, older individuals tend to have fewer T cells, and these T cells have a reduced proliferative capacity. The drop in T cell number can be accounted for in part by thymus atrophy that occurs with age (Aspinall and Andrew 2000; Imami et al 2000). In addition, T cells isolated from aged humans and mice are less responsive to a range of diverse stimuli. One feature of this reduced responsiveness is a significant reduction in NF-κB activation (after TNF-α, CD3 cross-linking, or phorbol myristate acetate stimulation) (Trebilcock and Ponnappan 1996; Ponnappan et al 1999a, b). The lower level of stimulated NF-κB activity in older T cells cannot be accounted for by the reduction in the NF-κB subunit expression. Instead, a deficiency at a step before IκB degradation appears to be involved. Evidence suggesting that changes in protein kinase activity may be responsible for the suppressed NF-κB activation in aged T cells has been reported. Protein kinase A has specifically been implicated in suppressing NF-κB activation in T cells isolated from older mice (Ponnappan et al 1999a, b). In addition, evidence that a lower level of proteasome activity in older T cells reduces their ability to degrade IκB-α has been obtained (Ponnappan et al 1999b). The mechanism by which age influences proteasome activity and other relevant signaling events in T cells is not known. It is interesting to note that in contrast to peripheral immune cells, cells in lymphoid organs of aged animals maintain higher levels of constitutive NF-κB activity (Spencer et al 1997). Whether or not these cells also respond more vigorously to strong NF-κB stimuli is not known. This latter finding does, however, highlight both the complexity of the aging process and the highly specific manner in which cells regulate their NF-κB activity.

In addition to suppressed T cell responses, certain components of the innate immune response are also decreased in older individuals (Butcher et al 2000; Lord et al 2001). Fc-mediated neutrophil phagocytosis is suppressed in older humans, as is Fc-mediated superoxide production (Fulop et al 1985). A number of macrophage functions are likewise suppressed in older individuals. Studies employing macrophages isolated from young and old rats have shown that MHC class II antigen presentation by macrophages is significantly decreased in older animals (Kizaki et al 2000). Moreover, older macrophages are less responsive to stimuli, generating less IL-1β and IL-6 after lipopolysaccharide stimulation, with a corresponding decrease in NF-κB activation (Kizaki et al 2000). The mechanism by which macrophages lose their ability to activate NF-κB can be explained in part by a decrease in the p65 subunit expression (Kizaki et al 2000). This decline in p65 corresponds with a drop in a population of macrophages expressing the E2 surface antigen (Kizaki et al 2000). Reduced antigen presentation and cytokine production by macrophages is likely to contribute to the loss of immune function in older rats. Whether a similar shift occurs in humans upon aging is not yet known.

Whereas the suppression of NF-κB activity in older immune cells is inarguably involved in the decline of the immune response, an issue that is left unresolved is the mechanism by which immune cell NF-κB activity is linked to age. A number of reports in the field have suggested that immunosuppressive glucocorticoids, which can inhibit NF-κB activation through a number of mechanisms (Heck et al 1997; Wissink et al 1997, 1998; Aljada et al 1999; De Bosscher et al 2000), may be responsible (Kizaki et al 2000). Although this is an attractive model, increased levels of glucocorticoids are not always observed in older individuals (Sonntag et al 1987; Goya et al 1989). Alternative mechanisms draw upon the telomere model of replicative senescence. A cell's capacity for proliferation is limited because chromosomal telomeres are shortened (in the absence of telomerase activity) with each round of DNA replication (Linskens et al 1995). One possibility is that continued expansion and contraction of T cell populations leaves older individuals with T cell populations with shortened telomeres and a dampened response to stimuli (Effros and Pawelec 1997; Spaulding et al 1997). (However, the influence of telomeres on immune dysfuntion during aging is keenly debated [Miller 2000].) Another model for aging of cells and organisms

is the oxidative stress model (Beckman and Ames 1998; Finkel and Holbrook 2000). In this model the accumulative oxidative damage of macromolecules in older cells interferes with their function, and ultimately cellular function and viability. Although enhanced oxidative damage of older immune cells may compromise their responsiveness to stimuli, this explanation is counterintuitive, given that NF-κB is sometimes stimulated by oxidative stress (Schreck et al 1991, 1992; Janssen-Heininger et al 2000). One possible resolution to this apparent contradiction is that chronic oxidative stress in older cells may trigger negative feedback responses that suppress NF-κB activation. For example, a modest increase in constitutive NF-κB activity induced through oxidative stress may increase IκB expression or may trigger other negative feedback mechanisms, which in turn dampen NF-κB activation by acute stimuli. Whether telomere shortening, oxidative stress, or some combination of events is responsible for suppressing the NF-κB activity and the immune response is not clear. What is clear is that identifying the pivotal changes responsible for the decline of the immune response with age would likely have enormous medical benefits for the elderly.

NF-κB ALTERATIONS OUTSIDE THE IMMUNE SYSTEM: THE UPSIDE AND THE DOWNSIDE

In contrast to the reluctance of older lymphocytes and macrophages to activate NF-κB in response to stimuli, analysis of other tissues has shown dramatic increases in constitutive NF-κB activity with age. In older rats and mice the NF-κB activity is significantly elevated in heart, liver, kidney, brain, and gastric mucosa (Geokas et al 1985; Helenius et al 1996a, 1996b; Korhonen et al 1997; Xiao and Majumdar 2000; Helenius et al 2001). In some instances, the age-induced increase in NF-κB DNA-binding activity can be suppressed by caloric restriction, linking the changes in NF-κB activity to life expectancy (Jolly et al 2001). The mechanism by which NF-κB is activated with age in these tissues is not known. Some results have shown correlations between NF-κB subunit expression and age (Helenius et al 1996a, 1996b). IκB levels are sometimes, but not always, found to be constitutively lower in older cells (Kim et al 2000; Xiao and Majumdar 2000). The transient nature of IκB degradation makes it difficult to rule out periodic rounds of IκB degradation and resynthesis in older cells (Brown et al 1993; Place et al 2001). The elevated levels of NF-κB activity in older tissues have sometimes been associated with increased cytokine expression, suggesting that NF-κB is being activated in response to proinflammatory signaling (Jolly et al 2001). This higher level of cytokine production, coupled with the progressive dysfunction of the immune response, may contribute to the development of inflammatory and autoimmune disorders associated with age. The enhanced NF-κB activity in older tissues may also be contributing to the development of another affliction of age: cancer.

NF-κB is presently receiving considerable attention for its potential role in carcinogenesis (Waddick and Uckun 1999; Mayo and Baldwin 2000; Baldwin 2001). By activating genes that can promote cell proliferation (eg, cyclin D1 and c-myc) and survival (eg, MnSOD and c-IAP), NF-κB may preserve and expand oncogenically initiated cells, thereby increasing the likelihood of cancer development. Interest in NF-κB's role in carcinogenesis has been heightened by the finding that it is an important downstream effector of the Akt kinase pathway (a pathway that is overactive in some forms of cancer)(Kane et al 1999; Ozes et al 1999; Romashkova and Makarov 1999; Madrid et al 2000). In addition, cell culture models suggest that NF-κB may antagonize gene activation by the p53 tumor suppressor protein, particularly when NF-κB is activated before p53 activation (Webster and Perkins 1999; Ikeda et al 2000). (When NF-κB is activated after p53, it may play a role in promoting apoptosis [Ryan et al 2000].) An attractive feature of NF-κB, with regard to its potential role in aging, is its activation by oxidative stress. Together with oxidative DNA damage, NF-κB activation may represent a potent strike in a devastating carcinogenic combination derived from cellular oxidation.

It is commonly accepted that the relationship between age and carcinogenesis involves the accumulation of somatic mutations that activate critical oncogenes and inactivate critical tumor suppressor genes (Fearon and Vogelstein 1990). The accumulation of mutations can result from exposure to environmental carcinogens that chemically modify DNA, but evidence is also accumulating that cancer development may be partly a consequence of reactive oxygen species generated as byproducts of normal cellular metabolic pathways (notably mitochondrial oxidative phosphorylation)(Breimer 1990; Loft and Poulsen 1996; Loft et al 1998). Reactive oxygen species and the resulting cellular oxidation products (such as malondialdehyde and 4-hydroxynonenal) can react with nuclear DNA to generate potentially mutagenic lesions (Esterbauer et al 1991). However, for carcinogenesis to proceed, DNA lesions need to be fixed into inheritable mutations by DNA replication. Moreover, initiated cells must overcome cellular checkpoints (such as the ARF-p53 pathway), which are designed to eliminate cells harboring activated oncogenes (Kamijo et al 1997; Zindy et al 1998). The ability of NF-κB to promote proliferation and survival may, therefore, serve to fix DNA lesions into mutations, protect cells against oncogene checkpoints, and facilitate cancer progression by promoting the propagation of genetically damaged cells. In this regard, oxidant activation of NF-

κB may be a potent sequelae to the oxidative DNA damage associated with aging.

Although the higher level of NF-κB activation associated with aging may be proinflammatory and carcinogenic, it is premature to conclude that NF-κB activation is deleterious in all instances. The ability of NF-κB to suppress cell death may help preserve tissue and organ function. A case in point is NF-κB activation during neurodegenerative disorders such as Alzheimer's disease (Boissiere et al 1997; Kaltschmidt et al 1997). The accumulation of amyloid-containing plaques and elevated levels of NF-κB activity accompany neurodegeneration during Alzheimer's disease. Cell culture modeling experiments have suggested that the antiapoptotic activity of NF-κB may in fact be beneficial in this instance: in vitro neurotoxicity by the amyloid β peptide is significantly suppressed by NF-κB (Behl et al 1994; Barger et al 1995; Terai et al 1996). Other instances in which NF-κB and its antiapoptotic function may be beneficial are neurodegeneration resulting from stroke and cell death after cardiac ischemia (Terai et al 1996; Ritchie 1998; Hill et al 2001). The proapoptotic role of NF-κB may also be beneficial for cancer prevention in the elderly: NF-κB activated after p53 activation has been reported to promote p53-induced cell death (Ryan et al 2000). However, a decisive statement on whether NF-κB is helpful or harmful in these instances in humans certainly requires additional analysis.

NF-κB AND AGING: THE CHICKEN OR THE EGG

The Holy Grail of aging research is the identification of the primary event triggering organismal decline and death. Tantalizing clues to this event have been provided by the analysis of simple organisms such as *Caenorhabditis elegans* and *Drosophila melanogaster* (Strauss 2001). Indeed, the extended life span of Drosophila that overexpresses Cu-Zn superoxide dismutase and catalase strongly supports the oxidative stress model of aging (Orr and Sohal 1994). However, the ultimate goal is not to increase the length of a bug's life, and extension of these studies to mammalian models and humans have been frustrating. Experiments attempting to extend the life span of rodents with antioxidants have failed (with the possible exception of spin-trapping compounds), leading pessimists to wonder whether oxidative stress is really a cause of aging or simply an effect (Beckman and Ames 1998). Telomerase also does not appear to influence aging under normal conditions (at least not in mice) because mice lacking telomerase activity do not have a shorter life span (Blasco et al 1997). Caloric restriction is of course an effective means of prolonging the life span in many organisms (perhaps by limiting oxidative stress [Ames 1989]), but the precise mechanism by which caloric restriction extends life is still very mysterious.

Given the general uncertainty about the aging process in mammals (and most of the current data), the changes in NF-κB activity observed with age are more safely categorized as an ''effect'' of aging, rather than a ''cause.'' For those interested in NF-κB, this conclusion should not dampen the enthusiasm for understanding the role NF-κB in age-associated diseases. As we all strive to achieve our maximum life span, we will undoubtedly encounter infection, inflammation, and possibly cancer. Here, knowledge of the precise role NF-κB is playing in these age-related diseases, and how its activity is being altered, may help alleviate the impact of these diseases and improve the quality of life.

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