Inflammation’s Effects on Aging

TASK GROUP DESCRIPTION

Background

Inflammatory processes are recognized in many chronic conditions that alter outcomes of health during aging, including atherosclerosis; dementias of the Alzheimer type; cancer; diabetes; chronic obstructive pulmonary disease; obesity; autoimmune disorders; and chronic viral, bacterial, and fungal diseases. Environmental factors include infectious agents and inflammmogens from air and diet. Conversely, clinical, experimental, and epidemiological lines of evidence have shown that anti-inflammatory drugs attenuate some of these conditions. In part, these synergies have been recognized in the National Institutes of Health director’s Gene, Environment, and Health Initiative (GEI) and in the National Institute of Environmental Health Sciences and National Human Genome Research Institute programs in environmental genomics. It seems timely and appropriate in the context of this conference to have a session on inflammation and aging. The scope should include human genomics and population diversity, multigenerational effects, and changing ecological factors. As urban populations continue to grow and as water and air quality deteriorate globally, we may anticipate increasing global exposure to infection and inflammation. The consequences to health during aging of the growing inflammatory burden have not been well articulated and new experimental approaches may be needed.

Initial Challenges to Consider

• What are the impacts of specific pro-inflammatory agents during the fetal, neonatal, childhood, pubertal, and reproductive periods of the life course on health during the last half of the life course?
• How will more discussion be developed between researchers and policy makers on biomedical interventions to aging and the industrial-ecological issues of air and water pollution?
• Will novel new agents evolve that are comparable to the late-life deleterious effects of microbial agents, such as type A beta-hemolytic streptococci or cigarette smoke?
• What are the trade-offs with the long-term administration of many pharmacological interventions, including anti-inflammatory agents? For example, low-dose aspirin can lead to fatal gastrointestinal or cerebral hemorrhages in susceptible individuals.
• Will physicians be able to take advantage of new genomic methodologies to predict who will or will not be at high risk for such side effects? More generically, can algorithms be developed to arrive at rational conclusions with regard to risk assessments for individuals and cost-benefit analyses for the case of populationwide interventions?
• Pharmaceutical companies are at high risk for costly lawsuits involving unanticipated serious complications of new drugs and vaccines, the development of which requires investments of millions of dollars. These are among the factors that discourage the development of new agents for infectious agents that are rare in the United States but are common in undeveloped countries. What business models (e.g., partnerships between industry and government) would address this problem?
Initial References


Task Group Members

• Abraham Aviv, University of Medicine and Dentistry of New Jersey
• Shea Gardner, Lawrence Livermore National Laboratory
• George A. Kuchel, University of Connecticut
• Sarah Kummerfeld, Stanford University
• J. Christopher Love, Massachusetts Institute of Technology
• Helen Vlassara, Mount Sinai School of Medicine
• Mary White, Centers for Disease Control and Prevention
• Allyson Collins, Massachusetts Institute of Technology

TASK GROUP SUMMARY

By Allyson Collins, Graduate Student, Science Writing, Massachusetts Institute of Technology

“Aging begins at fertilization,” said Caleb Finch, codirector of the University of Southern California’s Alzheimer’s Disease Research Center and professor in the
neurobiology of aging. The statement illustrated the enormity of the task for the seven others around the table—scientists, geriatricians, a public health official, and a chemical engineer—charged with evaluating inflammation's effect on aging. Finch, who inspired the topic selection, initiated conversation about the subject on day one of the National Academies Keck Futures Initiative Conference, and then left the group members to tackle the topic.

Narrowing the Problem

The first issue: oxidative stress (OS), the body’s inability to control high levels of cell-damaging reactive oxygen that is produced by metabolism. The process of aging in most mammals includes an increased burden of oxidative stress and inflammation, as well as a declining innate immunity. In humans, high OS and inflammation are both involved in many diseases of aging, including atherosclerosis, arthritis, cancer, Parkinson’s, and Alzheimer’s. But several group members asked what causes this burden on the body? Is it related to the environment, is it the result of an intrinsic problem, or is it just the nature of aging?

These fundamental questions led George Kuchel, chief of the Division of Geriatric Medicine and director of the UConn Center on Aging at the University of Connecticut, to ask: “Do we know that elevated peripheral inflammatory markers, which have been shown to predict disability, reflect the presence of tissue inflammation? Does this process drive the progression of disease, frailty, and disability? Should we be trying to eliminate inflammation, or does it actually reflect the body’s normal compensatory mechanism to injury?” These uncertainties remained an underlying thread in much of the discussion, and were soon joined by a host of others: From where do high oxidative stress and inflammation originate? Does high OS/inflammation cause age-related disease, or does it result from disease? At what age do the OS/inflammatory responses emerge?

It’s difficult to pin down both the source of oxidative stress and inflammation as well as their effects on the body because multiple issues are involved. When older adults present to their physicians, their problems cross the boundaries of organs, and inflammation is just one such systemic problem. Because this stress likely accumulates over many years, no explicit formula exists for calculating the increasing trend of oxidative stress and inflammation with age. Many interacting aspects contribute, including the endogenous factors such as metabolic and hormonal changes, gender, race, and genetic variation, and the exogenous factors such as diet, physical activity, environmental pollutants or irritants, socioeconomic status, and stress. Therefore, by reducing or eliminating these causes, age-related diseases could also decline, possibly resulting in an increased healthspan and ultimately a longer lifespan.

The group agreed on the complexity of the causes of OS/inflammation, and also on the dramatic changes in external stimuli over the past 30 to 50 years. Modern diets are higher in advanced glycation end products (AGEs), harmful compounds produced after consuming heated, sterilized, or processed foods, which may significantly contribute to oxidative stress and chronic diseases. Also, changes in our culture have brought about transformations in patterns of physical activity, socioeconomic status, stress, chronic infections, and the environment, all of which increasingly affect inflammation.

As the day progressed, ideas continued to flow, but group members struggled in pinpointing and defining the challenges involved. They also expressed frustration with
the narrowness of the topic. “We can redefine the questions as a group,” said Helen Vlassara, the appointed leader, and professor and director of the Division of Experimental Diabetes and Aging at Mount Sinai School of Medicine. “We’ve been given license for that.” Yet no one dared to propose an alternative. So the conversation continued but directed more toward possible remedies.

Identifying the Solutions

First, Abraham Aviv, professor and director of the Center of Human Development and Aging at the University of Medicine and Dentistry of New Jersey, approached the subject of low-grade inflammation in relationship to aging conditions such as cancer and cardiovascular disease. “Wouldn’t it be a great idea if we could find anti-inflammatory drugs that don’t have the side effects and could impact these diseases?” he asked. Then, Sarah Kummerfeld, a postdoctoral fellow at Stanford University spoke up. “We have an inbuilt system to upregulate antioxidants. Can we make that start working harder to induce the antioxidant system?” she suggested, in an effort to combat the oxidant stress.

And later, Kuchel attempted to summarize the conversation about inflammation therapies: “They can be highly targeted interventions, targeting specific organs, or they can be very broad, such as dietary manipulations, exercise, or improved living standards. Those are attractive precisely because they are pleotropic,” or have multiple effects, he said. Then, Mary White, an epidemiologist and branch chief in the Division of Cancer Prevention and Control at the Centers for Disease Control and Prevention, asked whether the scientific knowledge was sufficient to support population-based interventions, such as fortifying processed foods with a compound that could combat inflammation, or altering messages about a healthy diet to address oxidative stress.

But in the midst of the ideas, Vlassara mentioned that the base level of inflammation in humans might actually need to be redefined due to overexposure to oxidants. “The earlier we diagnose that, the earlier we can have an impact on decision making,” she said. So they changed gears and began considering long-term, population-based studies to track changes in factors related to inflammation over time. However, these studies require a well-defined insult to the system and a well-defined bodily reaction to track the physiological changes associated with oxidative stress. In addition, such a study done in a prospective manner might require 50 years or more to gain results.

By the end of the day the group had conferred about many ideas and possible solutions relating to the topic that they had previously considered to be narrow. When they regrouped the following morning, Vlassara announced the results of her PubMed search the previous night—more than 21,000 citations on inflammation and aging, indicating the overwhelming evidence on the subject. “We need to start coming to an agreement,” Kuchel said, and the topic turned to the role of gender in inflammation. Why is it that estrogen in most cases produces anti-inflammatory effects, but in some situations exhibits pro-inflammatory behavior? Approaching this issue in terms of gender naturally leads to questioning the effects of hormones on innate immune responses. The group proposed the naked mole rat, which doesn’t undergo menopause, as an animal model for studies of hormone effects and gender differences in aging inflammatory responses.

Aging animal models could also be the means for clarifying the cause-and-effect relationship between inflammation and age-related diseases. Through these models, disease burden could be linked with levels of inflammatory factors, internal and external
oxidant pressures could be studied, and profiles of OS/inflammatory changes could be established. Information gained from these types of studies could be used to predict the onset of disease. “Our priority needs to be linking these factors to disability,” Kuchel noted. “We’re not here to address a specific disease or condition. We’re here to address what we can do to increase people’s health and functional independence as they age.”

So the group returned to human studies and the topic of diet. They suggested that additional research could focus on cross-sectional, longitudinal analyses of AGE-restricted diets, and diet’s effect on chronic inflammatory diseases. The results could also affect nutritional policies in the future—guidelines could be instituted for disclosing AGE content in food products, and limits could be imposed on the total amount of AGEs allowed.

A diagnostic tool that might be used to test for reactive oxygen species and AGEs is called an enzyme-linked immunosorbent assay, or ELISA. High-throughput screening methods could also be put into place to detect inflammatory markers and DNA mutations induced by particular inflammogens. Further analysis could involve the relationship of these factors to problems with blood vessels, loss of muscle mass, and general age-related weakness.

Another hot topic became the telomeres at the tips of chromosomes. Aviv explained to the group that in white blood cells, the length of telomeres decreases as the cumulative burden of oxidative stress in the organism increases. Future research could clarify the relationship between inflammogens and the length and functioning of telomeres in the aging immune system.

Next, Aviv suggested that the group consider developing diagnostic tests to distinguish between inflammation and oxidative stress, and to analyze biomarkers linked to the conditions. This gave Kuchel an idea: establishing an OS/inflammation equivalent of Koch’s postulates, which in 1890 outlined the criteria for determining that a specific infectious organism caused a disease. This, however, has been determined in many studies in animals and several in humans.

Discussing the Limitations

With the conference winding down, the group began considering the limits of current technology that would need to be overcome before implementing these solutions. First, the members noted that technology for assessing inflammatory markers in the clinic is unavailable. Physicians need low-cost, minimally invasive, rapid methods for analyzing reactive oxygen species and AGEs that could be performed during annual physicals. This type of system could even lead to home-based monitoring of OS markers, similar to diabetic kits for tracking glucose levels. In addition, a comprehensive database of genetic, protein, and metabolic data from a diverse human population is also lacking.

Near the end, Finch, the inspiration behind the topic, returned. “Our effort . . . can stimulate general discussion on the topic,” he said, offering encouragement to the smallest group at the conference, its participants mixed with both basic and clinical research backgrounds. Each member offered a fresh perspective on the topic of inflammation and aging, and each left with a detailed list of questions and a variety of solutions that may not have been conceived without this interdisciplinary experience.