A gripping reality: oxidative stress, inflammation, and the pathway to frailty

CLINICAL INVESTIGATORS within the field of geriatric medicine aim to get a handle on “frailty.” That aging is an inevitable consequence of staying alive is irrefutable, but why some people manage to do so and maintain stature and function, while others do not, remains an unresolved question. Frailty is a term commonly used to describe individuals with physical and functional decline that occurs as a consequence of certain diseases (e.g., cancer, chronic infection, etc.) but also even without disease (Fig. 1). The condition has been hard to define because of the seemingly insurmountable heterogeneity inherent in geriatric populations on the basis of variable rates of organ system decline and the presence or absence of any of a number of diseases. Yet, no matter the pathway taken to frailty, the clinical picture has common features, including a reduction in lean body mass (sarcopenia), osteopenia, cognitive impairment, and anemia. On the basis of data derived from large cohorts of elderly individuals, Fried and colleagues (3) have offered an operational definition of frailty incorporating an assessment of five specific characteristics, each of which is ascribed a score of 0 if absent or 1 if present (Table 1). A score of 3 or more has been shown to be independently predictive of a range of adverse clinical outcomes, including acute illness, falls, hospitalization or nursing home placement, and early mortality (1–3).

With the phenotype better defined, attention has shifted to pathophysiology. Although frailty may occur in the absence of a diagnosable illness, the fact that some become frail, and others do not, suggests an inherent or acquired variability in homeostatic pathways. Recent evidence from observational studies has raised suspicion that dysregulated inflammatory processes are involved in, if not central to, the variable patterns of aging. Elevated serum levels of certain proinflammatory cytokines, most notably IL-6, are increasingly present with advancing age and to a greater extent with frailty (4). Furthermore, the appearance of this and other inflammatory markers has been associated with a number of adverse clinical outcomes, including decreased strength and mobility, falls, and mortality (5).

Of the salient features of frailty, sarcopenia is prominent (6). Weakness, fatigue, imbalance, altered gait, and speed can all be related to diminished skeletal muscle mass (7). Just why this occurs has not been established. Included for consideration is an age-associated reduction in anabolic steroids (testosterone), malnutrition, immobility, lack of exercise, and inflammation. Yet the overlap is remarkable. For example, inflammatory signals, such as TNF-α, viral antigens, bacterial products, or reactive oxidative species (ROS), will stimulate IL-6 and other inflammatory modulators, most commonly by activating NF-κB, resulting in expression of several proteins instrumental in inflammatory and proliferative responses. In addition, increased NF-κB activity might also be the result of postmenopausal estrogen or androgen decline. For example, testosterone has been shown to inhibit IL-6 expression primarily by stabilizing the inhibitor protein-κB (IκB)-NF-κB complex, reducing nuclear translocation and gene activation (8). Estrogen is thought to mediate its anti-inflammatory effects by an analogous manner (9). To the extent that these sex steroids decline with age, increased NF-κB activity may result.

That NF-κB overexpression is relevant to muscle wasting is supported by the recent experiments in mice genetically engineered to be deficient in the kinase responsible for inactivating the IκB inhibitor and allowing NF-κB to transcribe its portfolio of inflammatory mediators. In a denervation paradigm, IκB kinase 2 (IKK2) knockout mice had less muscle atrophy and maintained fiber type, size, and strength with less protein degradation than the wild-type controls. Furthermore, in response to muscle damage by toxic chemical injection, IKK2 knockouts had improved skeletal muscle regeneration and reduced fibrosis (10).

Thus it appears that the same inflammatory pathways implicated in many of the common features of frailty are also involved in skeletal muscle homeostasis. One specific mechanism whereby this might occur is the inhibition of the transcription factor MyoD by NF-κB. MyoD is a member of the myogenic basic helix-loop-helix transcription factor family, and in experimental animals, its absence is associated with diminished muscle repair after injury (11).

Thus, when deciphering the mechanisms of age-related or inflammation-related sarcopenia, one could readily be satisfied that the answer resides with the increased activity of NF-κB, resulting in a metabolic picture of increased catabolic and decreased anabolic forces exerted within muscle cells (Fig. 1). That other explanations are involved, however, is suggested by the work of Howard et al. in this issue of the Journal of Applied Physiology (12). By capitalizing on a well-characterized epidemiological cohort of frail or near-frail individuals (Women’s Health and Aging Study I), the hypothesis that sarcopenia present in the more frail participants was related to the extent of ROS-induced direct muscle damage was indirectly tested by the measurement of protein carbonylation (an indicator of ROS muscle damage) and grip strength (as a marker of overall muscle mass). Such simple and logical hypotheses are often difficult to prove. With the caveat that conclusions derived from both observational and cross-sectional data, the findings are quite intriguing and support a “direct-hit” hypothesis. One might argue that protein carbonylation is not an ideal reflection of protein oxidation, or that grip strength is an insufficient reflection of overall muscle mass. Yet, both seem to be quite accurate. We have known that protein carbonyl levels increase with age and that grip strength declines. Howard and colleagues provide evidence that these occurrences are related. Those with the highest protein carbonyl level were demonstrably lowest on the grip strength test.

Gerontologists have focused on oxidative stress for decades, and most agree that with time there is an accumulation of DNA, muscle, and lipid damage sufficient to impair cellular and organ function. What is neat about the Howard study is the simple correlation of a measure of protein oxidation and muscle strength in a well-characterized elderly population, many of whom were frail. Thus the “free radical” gerontologists do not necessarily have to implicate inflammatory mechanisms to account for sarcopenia (although such are likely to be contributory). Furthermore, the results imply that environmental and nutritional efforts to modify oxidative damage may, in
Fig. 1. Pathways to sarcopenia. Reactive oxygen species increase with age, as does the presence of inflammatory processes, resulting in both catabolic and anabolic effects on muscle. Oxidative stress may also directly injure muscle, as suggested by Howard et al. (12), contributing to the composite picture of sarcopenia and frailty in some, but not all, elderly. AP-1, activator protein 1; CRP, C-reactive protein.

Table 1. Criteria of Fried et al. for an operational definition of frailty incorporating an assessment of five specific characteristics

<table>
<thead>
<tr>
<th>Domain</th>
<th>Criterion</th>
<th>Frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional status</td>
<td>Unintentional weight loss, last 12 mo</td>
<td>&gt;5% body weight</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>Grip strength/stratified by sex and BMI</td>
<td>Men &lt;29–32 kg/m²; women &lt;17–21 kg/m²</td>
</tr>
<tr>
<td>Lower extremity performance</td>
<td>Walking speed, 15-ft walk/stratified by height</td>
<td>Men &lt;383 kcal/wk; women &lt;270 kcal/wk</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Based on the short version to the Minnesota Leisure Time Activity questionnaire, kcal/wk calculated</td>
<td>Subjects answering “2” or “3” to either of these questions</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>Using CES-D Scale; the following statements are read: a) I felt that everything that I did was an effort; b) I could not get going. The question is asked, “How often in the last week did you feel this way?” 0 = rarely; 1 = some or a little of the time (1–2 days); 2 = a moderate amount of time (3–4 days); 3 = most of the time</td>
<td>Subjects answering “2” or “3” to either of these questions</td>
</tr>
</tbody>
</table>

BMI, body mass index; CES-D Scale, Center for Epidemiological Studies-Depression Scale. See text for further description of scoring. Adapted from Fried et al. (3).

the long run, reduce the likelihood of developing this important component of frailty.

REFERENCES


William B. Ershler
Clinical Research Branch
National Institute on Aging
Harbor Hospital
Baltimore, Maryland
e-mail: ershlerwi@mail.nih.gov