IMMUNOBIOLOGY

Comment on Mirandola et al, page 2418

Killer cells protect themselves

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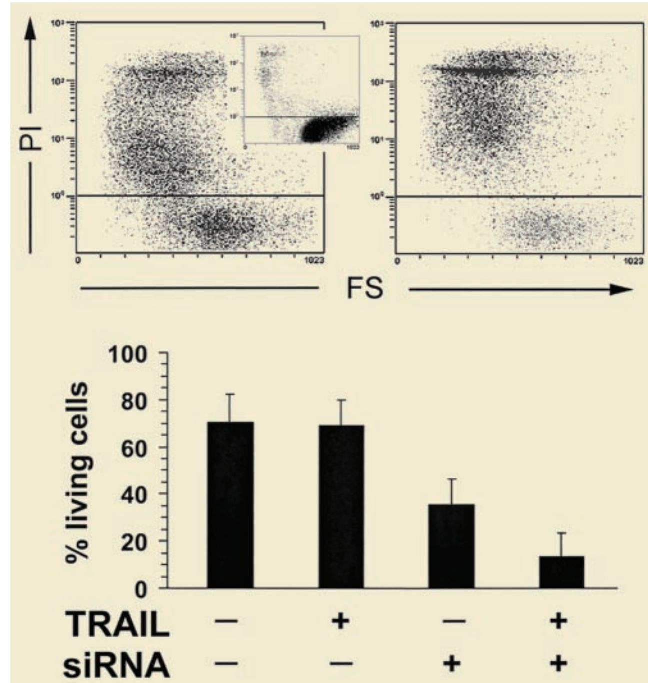
The importance of the report by Mirandola and colleagues is that the data may explain why natural killer (NK) and CD8$^+$ T cells can survive despite liberating death receptor ligands and secretory granule contents.

This may be related to the phenomenon of the "veto" function of NK and CD8$^+$ T cells (ie, elimination of precursors of cytotoxic T lymphocytes [CTLs][1-3] directed against these cytotoxic cells). They observe that activated human NK and CD8 T cells express TRAIL (tumor necrosis factor [TNF]–related apoptosis-inducing ligand) and TRAIL receptors but are not lysed by TRAIL. The primary mechanism of resistance to TRAIL is the expression of c-FLIP (cellular Fas-associated death domain protein [FADD]–like interleukin 1 [IL-1]–converting enzyme [FLICE]–inhibitory protein). The investigators observed that NK and CD8$^+$ T cells expressed mRNA for the functional (R1 and R2) and decoy (R3 and R4) TRAIL receptors. TRAILR4 was expressed on the cell surface of resting and activated NK and CD8$^+$ T cells, whereas R2 was expressed only after activation with cytokines. R1 and R3 were not expressed on the cell surface and this was associated with less mRNA. Soluble TRAIL induced apoptosis of control Jurkat and HL60 cell lines, which was blocked by TRAIL-R1 and -R2-Fc chimera molecules. However, resting control or activated NK and CD8$^+$ T cells were resistant to additional apoptosis over the background levels. Treatment of both NK and T cells with actinomycin D to prevent new protein synthesis rendered them sensitive to TRAIL-induced apoptosis. The major protein that provided protection was c-FLIP because transfection of NK or T cells with siRNA specific for c-FLIP mRNA abrogated the resistance to TRAIL.

A significant feature of TRAIL is its selective destruction of tumor cells, sparing most normal cells.[4] It will therefore be important to determine if some normal or tumor cells not lysed by TRAIL express TRAIL receptor R1 or R2 but are protected by the same or similar mechanism described in this report. ■



TRAIL-induced apoptosis of IL-2–activated NK cells (10 days) in the presence of anti-FLIP siRNAs. See the complete figure in the article beginning on page 2418.

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CLINICAL OBSERVATIONS

Comment on Guralnik et al, page 2263

It's tough to be old and anemic

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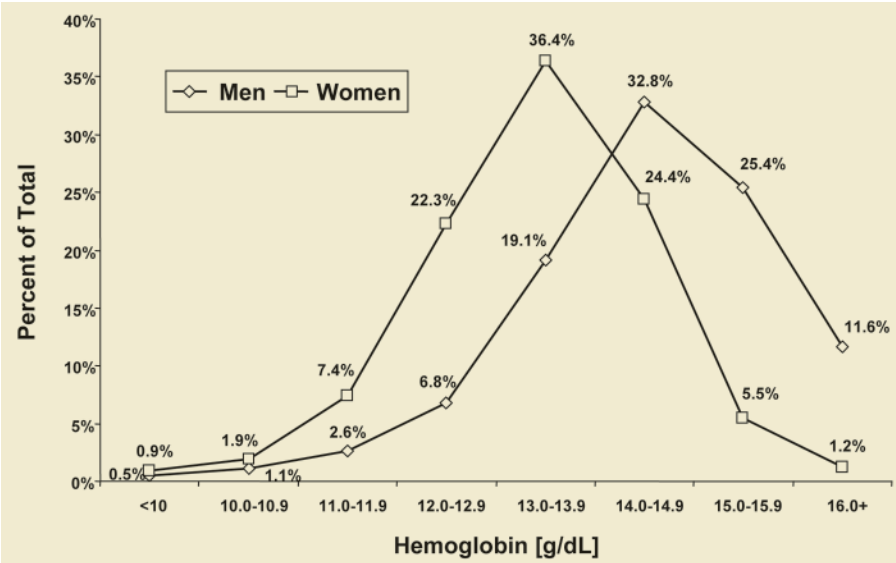
This seemingly simple study is in fact quite provocative because it argues that the usually mild anemia, frequently ignored, that occurs in about 10% of subjects older than 65 years may have serious clinical consequences.

The thrust of the article by Guralnik and colleagues is that anemia, as defined by World Health Organization (WHO) criteria, is very common in those older than 65 years; it is mostly mild anemia, but it should not be considered to be a normal event in the aging process and may have important pathophysiologic consequences. The data are provided by the Third National Health and Nutrition Examination Survey (NHANES III). The importance of this survey is that it obtained hemoglobin levels on representative subjects living in the community, of whom almost 4200 were older than 65 years. And of this group, 2096 subjects had further tests to characterize the anemia. The WHO criteria for anemia in adult men is a hemoglobin (hgb) level less than 130 g/L (13 g/dL) and for adult women a hgb level less than 120 g/L (12 g/dL). Using these WHO criteria, the prevalence of anemia in men older than 65 years is 11% and for women it is 10.2%. But this apparent similarity in prevalence rates is dependent on the cut point used because 32.5% of women older than 65



Distribution of hemoglobin in persons 65 years and older according to sex. See the complete figure in the article beginning on page 2263.

years have hgb levels less than 130 g/L (13 g/dL). While it makes sense during childbearing years to consider sex-different normal hgb levels, is that still the case for those older than 65 years? Of equal interest is the striking ethnic difference, with 3 times as many non-Hispanic blacks of either sex older than 65 years having anemia. It is not clear at this time whether this is a consequence of comorbidities, has a deleterious clinical impact, or is a normal ethnic difference. The anemia in this aging population is usually not severe, with only 2% to 3% of subjects having hgb levels less than 110 g/L (11 g/dL), and as such is frequently ignored. Reference is made to a population-based study of elderly subjects with hgb levels less than 110 g/L (11g/dL) where the diagnosis of anemia was listed in only a quarter of their medical records. The key question then is whether this seemingly casual acceptance of mild anemia in the elderly has a clinical consequence. The authors argue that anemia is not a normal consequence of aging and that even these mild levels of anemia indeed have an impact on morbidity and mortality. They cite literature showing that even very mild anemia impairs physical performance and leads to adverse outcomes in patients with acute myocardial infarction and congestive heart failure. The survey also comprised studies designed to identify the cause of the anemia in the aged, although absolute reticulocyte counts, erythropoietin levels, and blood smears were not part of the analysis. The most frequent causes of the anemia were iron deficiency, chronic renal failure, and ACI (anemia of chronic inflammation; formerly ACD). Many of the subjects were also vitamin B_{12} and folate deficient, although it is not clear that the level of these nutritional deficiencies was sufficient to contribute to the cause of the anemia. A substantial number of cases were classified as unexplained anemia (UA), which lead the authors to wonder if there was an entity of anemia in the aged, perhaps related to defective hypoxia sensing. Further studies are needed to determine if correction of the mild anemia perhaps using erythropoietin will improve the outlook of affected patients. ■

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