New Role for the Mitochondrial Peptide Humanin: Protective Agent Against Chemotherapy-Induced Side Effects

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The remarkable advances made over the last several decades in the form of effective therapies that have substantially reduced the mortality from various malignancies, particularly those affecting pediatric patients, has presented the medical community with new challenges of dealing with cancer chemotherapy side effects. Cancer survivors, especially those who were treated for their cancer as children or adolescents, are frequently afflicted with various endocrinopathies, infertility, and growth impairment (1). Current adjuvant therapies that have been approved for dealing with chemotherapy side effects mainly address acute symptoms, such as nausea, and bone marrow renewal. There are multiple cancer drugs that cause damage to the growth plates of growing bones and currently can only be dealt with through later treatment with growth hormone and with variable results (2).

The findings in the article by Eriksson and colleagues in this issue of the Journal (3) show that bortezomib-induced growth failure in mice was almost completely ameliorated by cotreatment with an analog of the mitochondrial-derived peptide humanin, while not interfering with the antitumor effects of bortezomib. Although not approved in children, bortezomib holds promise in childhood leukemia and other cancers affecting growing children, but among its most worrisome side effects in this population is the toxic effect on the growth plate. These investigators showed that a 2-week treatment with this recently approved proteasome inhibitor was quite effective in reducing the growth of neuroblastoma xenografts; however, it dramatically arrested bone growth in the host mice. Cotreatment with intraperitoneal injections of a humanin analog twice a week reversed the growth arrest but maintained the tumor-inhibitory effect of bortezomib. The effects of humanin on tibia growth occurred, at least in part, by protecting the cells in the growth plate from bortezomib toxicity. This phenomenon is reminiscent of the concept of differential protection, whereby an intervention protects from the toxic effects of chemotherapy on healthy host organs while enhancing its killing effects on cancer cells, which was first proposed by Longo and colleagues using fasting (4).

Mitochondria are central to multiple biological processes, including energy metabolism, apoptosis, and the integration of oxidative stress (5), and mitochondrial dysfunction is a hallmark of aging and multiple aging-related diseases from diabetes to dementia. The mitochondrial peptide humanin was discovered more than a decade ago nearly simultaneously by three different groups who cloned an open-reading frame from the mitochondrial 16S rRNA region encoding a 24-aminoacid peptide with potent neuroprotective (6), antiapoptotic (7), and IGFBP3-binding cytoprotective effects (8). Since then, the protection induced by humanin has been shown to be wide ranging, acting on various brain disorders, metabolic abnormalities, and cardiovascular diseases such as atherosclerosis (9), and has now been extended to include the bone growth plate (3). Understanding the biology of humanin remains an exciting scientific challenge, and its functions as a retrograde signal from the mitochondria are still being unraveled (10). Clearly, part of the effect of humanin involves a systemic metabolic normalization of stress-response homeostasis (11). An additional mechanism of humanin action involves reduction of inflammation (12), and humanin signals through at least two receptors (10), one of which is the immunity-modulating protein-coupled formyl-peptide receptor-like-1 (13). There are several pathways, therefore, including the direct involvement of mitochondrial damage and its amelioration by humanin, that may explain its ability to abrogate chemotherapy side effects (14). It is also interesting to speculate which pathways are involved in the direct inhibition of tumor growth observed in the article by Eriksson and colleagues (3). The observation that humanin antagonizes the proapoptotic Bax (7) initially led to concerns that it might be tumor promoting; however, the reassuring data that it is actually tumor inhibiting require further investigation into its potential role in cancer biology.

All of this underscores the potential for humanin analogs as cancer chemotherapy side-effect prevention treatments. Such adjuvant approaches could be useful to prevent not only growth plate damage but also toxicity to other systems where humanin has been shown to have protective effects, such as testicular infertility (15), as well as “chemo-brain”, neuropathy, endocrinopathies, and cardiomyopathy. In Figure 1, the interface between chemotherapy, affected host organs, the tumor, and the mitochondrial peptide humanin is described. The promising application of humanin-based therapies to combat chemotherapy-related side effects, as well as a host of diseases, such as Alzheimer’s disease, diabetes, and atherosclerosis, may require further improvements in the potency and pharmacokinetic characteristics of the peptide and thorough preclinical development, but the findings of Ericsson et al. (3) provide a clear rationale for such an effort.
Figure 1. Humanin protects from chemotherapy-related toxicity. The mitochondrial-derived peptide, humanin, is encoded within the mitochondria and is secreted in response to cellular stress (A). Both endogenous and exogenous humanin protect a variety of organs such as brain and bone from oxidative stress, age-related damage, amyloid accumulation, and the toxic effects of chemotherapy (B). Through as of yet unknown mechanisms, humanin administration delays tumor progression (C).

References

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