Reply to Turner and Kerber

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TO THE EDITOR: This letter is a response to the commentary by Drs. Ralph J. Turner and Irwin J. Kerber (7) regarding my review article (8) in *Physiological Genomics*. I thank Drs. Turner and Kerber for their interest and encouraging remarks on the review article. I applaud their enthusiasm in applying basic research to clinical practice and am pleased that my paper provided some insights into their observations in the clinic.

Clinical studies, such as those on Alzheimer’s disease and coronary heart disease, do indeed suggest that health status or age at initiation of treatment may contribute to severity of the side effects of estrogen replacement therapy (ERT) (1, 2). Preliminary results from the Kronos Early Estrogen Prevention Study (KEEPS) also suggest that ERT in newly menopausal women has moderate beneficial effects with little side effects (4), as opposed to the numerous detrimental effects of ERT in older women (>65 yr old) included in the Women’s Health Initiative (WHI) studies (6). These data support the idea that ERT is beneficial and less detrimental within a “critical window of time” and that better estrogen response may be expected from a “healthy cell” than a damaged cell (2). While these studies do support the critical window and healthy cell hypotheses, some studies also suggest that the length of exposure, rather than the time of treatment or status of the cell, is a better predictor of estrogen response (3). Experiments must then be focused to validate these hypotheses.

It is very clear that estrogen has pleiotropic actions on gene regulation and cell signaling, depending on cell type and cell context, such as time of treatment, type of estrogen receptors, and presence of specific cofactors (5). However, the contribution of a healthy vs. a damaged cell on estrogen action warrants a thorough investigation. Studying the pleiotropic actions of estrogen in this context may help prove or disprove the critical window and healthy cell hypotheses.

Mitochondrial dysfunction can transform a healthy cell into a damaged cell, which may potentially influence estrogen action (8). Unfortunately, there are currently no clinical data demonstrating that mitochondrial dysfunction increases the severity of the side effects caused by ERT. Identifying mitochondrial dysfunction in humans, and what type of dysfunction can influence estrogen action, also remains a challenge. However, studying mitochondrial function and its role on estrogen response may help validate the healthy cell hypothesis. Once proven, evaluation of mitochondrial function could then potentially serve as a diagnostic tool for identifying good candidates of ERT.

DISCLOSURES
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REFERENCES

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