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Citation: Baur, J. A. et al. "Dietary Restriction: Standing Up for Sirtuins." Science 329, 5995 (August 2010): 1012–1013 © 2010 American Association for the Advancement of Science

As Published: http://dx.doi.org/10.1126/science.329.5995.1012

Publisher: American Association for the Advancement of Science (AAAS)

Persistent URL: http://hdl.handle.net/1721.1/116434

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

Published in final edited form as:
Science. 2010 August 27; 329(5995): 1012–1014. doi:10.1126/science.329.5995.1012.

Dietary Restriction: Standing Up for Sirtuins

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L.P.G. and D.A.S. are co-chairs, and S.I. and E.V. are members of the scientific advisory board for Sirtris, a GSK company. D.A.S. owns shares in GSK. E.N.C. has a sponsored research agreement with Sirtris/GSK. R.d.C. has a cooperative research and development agreement with Sirtris/GSK. All other authors declare that they have no conflicts of interest.

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We believe that L. Fontana, L. Partridge, and V. D. Longo should have included a discussion of sirtuins in their Review “Extending healthy life span—From yeast to humans” (16 April, p. 321). We also believe that some of the references used are misleading.

The authors state that the purpose of their Review is to “consider the role of nutrient-sensing signaling pathways in mediating the beneficial effects of dietary restriction.” Yet there was no mention of the sirtuins, a family of critically important nutrient-sensing proteins that promote health span from yeast to mammals, as shown by more than 1000 peer-reviewed publications from labs around the world. The authors state that “[i]t is unlikely that a single, linear pathway mediates the effects of dietary restriction in any organism,” and we agree. Indeed, the aging field now recognizes that healthy life span is under the influence of several nutrient-sensing pathways, and there is at least as much evidence for the involvement of sirtuins in the dietary restriction response as for any of the pathways discussed in the Review (1).

Numerous independent studies show that dietary restriction does not extend life span when sirtuins are deleted. This result has been shown in multiple organisms, from yeast to flies and even in mice (2). Moreover, deleting SIRT1, SIRT3, SIRT4, or SIRT5 abrogates various physiological aspects of dietary restriction and fasting, including longevity (3). SIRT1 activity in mice increases during dietary restriction, and enforced SIRT1 activity results in a dietary restriction–like physiology and protection from many of the same degenerative diseases that are protected by dietary restriction in mice, including cancer, neurodegeneration, inflammatory disorders, metabolic syndrome and type 2 diabetes, and cardiovascular disease (4). In humans, there is also evidence that sirtuins may be involved in mediating the response to dietary restriction and increasing health span. For example, SIRT1 levels increase in humans practicing dietary restriction (5), and there are strong associations between alleles that increase SIRT1 expression and increased metabolic rate, as well as protection from type 2 diabetes (6).

Collectively, these studies provide strong support for a central role of sirtuins, as well as other nutrient-sensing proteins, as mediators of the effects of dietary restriction and the extension of healthy life span.

We also believe that the Review fails to assign due credit for major discoveries in the aging field, and not just from the sirtuin field. In some cases, credit is incorrectly attributed. For instance, the ablation of *Drosophila* germ line as it affects insulin-like peptides (dlps) and

life span was performed by Flatt *et al*. (7). In another instance, data is selectively used to support the view that insulin signaling plays a role in dietary restriction, which is the opposite of what the original paper shows (8).

The Review shows dietary restriction working through insulin signaling in nematodes and flies, both of which are controversial. Studies indicate that daf-16/FoxO is not required for life-span extension by dietary restriction in nematodes (9) or in flies (8). Published data further demonstrate that dietary restriction robustly extends fly life span even when RNAi has suppressed diet-associated changes in insulin-like peptides.

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