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COMMENT ON WU AND SPIEGELMAN

Irisin ERKs the Fat. Diabetes 2014;63:381–383

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Wu and Spiegelman (1) summarized recent findings on the signaling, the putative receptor, and the physiological implications of the new myokine irisin for both rodents and humans. Overall, they state that irisin may be of great interest as a human therapeutic due to the activation of a thermogenic gene program in adipocytes (1). Irisin is cleaved from FNDC5, a type 1 membrane protein that was originally reported to be upregulated in response to exercise in both mice and men (2). However, a comprehensive analysis of published data challenges the translation of the irisin concept to humans (3).

Thus, the regulation of FNDC5 gene expression could not be reproduced by the majority of human studies using a variety of exercise protocols (3). Further, 12 out of 15 published studies failed to prove an effect of exercise on circulating irisin in humans (3). We recently reported that a mutation of the canonical ATG start site of the human FNDC5 gene results in a substantially reduced translation efficiency and potentially the production of truncated forms of FNDC5 (4) in humans. Published studies assessing irisin in human circulation are subject to a huge variation, not allowing any solid conclusion on the nature and concentration of irisin in human blood. Using a mass spectrometry approach, a unique peptide located in the irisin sequence was identified in a FNDC5-immunoreactive band in human serum samples, not ruling out the presence of different FNDC5 fragments (5). In fact, the peptide is present in the truncated form of FNDC5 described by Raschke et al. (4). Overall, the concentration and nature of circulating FNDC5 fragments in humans remain unclear.

Finally, very few data exist regarding the relevance of irisin as an inducer of browning in humans. Lee et al. (5) were the first to assess the potency of FNDC5 to induce browning in primary human adipocytes from different depots. Whereas adipocytes isolated from neck biopsies exhibited a very prominent activation of a thermogenic program, adipocytes isolated from subcutaneous and omental depots were only marginal or unresponsive (5). This fully agrees with our inability to demonstrate browning of human subcutaneous adipocytes in response to FNDC5/irisin (4). This suggests that only a small subpopulation of adipocytes highly expressing brite-specific markers is mediating the irisin effect. In light of these considerations, the role of irisin in humans appears questionable.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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