Muscle secretory factors - where are we at a decade later?

M.A. Febbraio, Cellular & Molecular Metabolism Laboratory, BakerIDI Heart and Diabetes Institute, Melbourne, VIC 3004, Australia.

Almost 50 years ago Goldstein (1961) proposed the hypothesis that muscle cells possess a “humoral” component that contributes to the maintenaince of glucose homeostasis during exercise. Approximately ten years ago, we identified skeletal muscle as a cytokine-producing organ, demonstrating that the metabolic and physiologic effects of exercise may be mediated by muscle derived humoral factors (for reviews see Pedersen & Febbraio, 2008, 2012). We have demonstrated that interleukin-6 (IL-6) was the prototypical “myokine”, up-regulated by muscle contraction and released from contracting skeletal muscle, to play important roles in lipid and glucose metabolism in metabolically active tissues. Other subsequntly identified myokines, such as irisin (Boström *et al.*, 2012), were made serendipitously, but it is likely that contracting skeletal muscle produces many myokines that positively act on the metabolism of other organs, presenting novel targets for therapeutics in the treatment of obesity related diseases such as type 2 diabetes.

We are currently using gene arrays and quantitative proteomic analyses to identify novel myokines that may play a biological role in energy metabolism and may aid in the development of identifying new drug targets to treat obesity related disorders. The finding that the muscle secretome appears to consist of several hundred secreted peptides provides a conceptual basis and a whole new paradigm for understanding how muscles communicate with other organs such as adipose tissue, liver, pancreas, bones and brain. We suggest that physical inactivity may lead to an altered myokine response, explaining why lack of physical activity is a cause of a whole network of diseases. The role of contraction-induced muscle derived secretory proteins thus gains importance.

Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Boström EA, Choi JH, Long JZ, Kajimura S, Zingaretti MC, Vind BF, Tu H, Cinti S, Højlund K, Gygi SP, Spiegelman BM. (2012) A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* **481:** 463-468.

Goldstein MS. (1961) Humoral nature of hypoglycemia in muscular activity. *American Journal of Physiology* **200:** 67 –70.

Pedersen BK, Febbraio MA. (2008) Muscle as an endocrine organ – focus on muscle-derived IL-6. *Physiological Reviews* **88:** 1379-1406.

Pedersen BK, Febbraio MA. (2012) Muscle, exercise and obesity: skeletal muscle as a secretory organ. *Nature Reviews Endocrinology* **8:** 457-465.

Supported by Grants from the NHMRC and DART.