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METABOLISM

Exercise resistance decoded

Even though the beneficial effects of exercise on health are well known, not everybody derives similar benefits from training in terms of endurance capacity and metabolic health.

In a new study published in *Nature Medicine*, Hirofumi Misu and colleagues show that the hepatokine selenoprotein P mediates exercise resistance in mice via its receptor in muscle (low-density lipoprotein receptor-related protein 1; LRP1). The finding that an endogenous liver-secreted factor inhibits the effects of exercise contrasts with the previously held notion that exercise resistance is determined at or before birth.

Mice globally deficient in selenoprotein P or with muscle-specific knockout of *Lrp1* (*Lrp1*$^{-/-}$) fed a high-fat diet for 1 month (to induce obesity) and then subjected to exercise training (treadmill; 30 min per day for 5 weeks) exhibited greater aerobic exercise capacity in endurance tests than did trained wild-type mice. The 'super-endurance' phenotype of both knockout mice was accompanied by increased phosphorylation of AMPK and expression of *Ppargc1a* (which encodes PGC1α) in skeletal muscle, which were mediated by increased production of reactive oxygen species. Conversely, AMPK phosphorylation and *Ppargc1a* expression induced by a single bout of exercise was suppressed in *Lrp1*$^{-/-}$ mice pretreated with selenoprotein P. Importantly, in a cohort of 31 sedentary, postmenopausal women without obesity or type 2 diabetes mellitus who underwent aerobic exercise training (walking and cycling; 3 days per week for 8 weeks), increased pre-training plasma levels of selenoprotein P were shown to be predictive of the ineffectiveness of training on endurance capacity.

While highlighting the therapeutic potential of targeting the selenoprotein P–LRP1 axis for treating metabolic diseases associated with a sedentary lifestyle, the findings also raise the possibility that selenoprotein P could modulate exercise responsiveness in situations other than overnutrition-related conditions, such as ageing-related exercise resistance.

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ORIGINAL ARTICLE Misu, H. *et al.* Deficiency of the hepatokine selenoprotein P increases responsiveness to exercise in mice through upregulation of reactive oxygen species and AMP-activated protein kinase in muscle. *Nat. Med.* http://dx.doi.org/10.1038/nm.4295 (2017)