What are the benefits of being big?

PERSPECTIVES

What are the benefits of being big?

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Like all eukaryotic cell types, skeletal muscle can store free fatty acids (FFAs) as triacylglycerol (TG) in lipid droplets (LDs), which in three dimensions can be viewed as balls of lipid ranging in size.

Excess ectopic fat storage in LDs is associated with impeded cell function. In sedentary individuals, compromised insulin sensitivity is commonly reported in muscle cells with abundant ectopic fat content. This contrasts with observations in trained athletes who are highly sensitive despite having numerous LDs. Typically LDs are decorated with a variety of proteins (including proteins of the perilipin (PLIN) family) involved in regulating lipid synthesis and degradation (jointly referred to as LD dynamics) (Badin *et al.* 2013). The set of proteins involved in LD dynamics is under the control of the exercise-inducible transcriptional co-factor PGC1α (Koves *et al.* 2013). Thus, muscle fibre type specific differences in LD dynamics exist and trained individuals possess higher levels of PLIN proteins and other LD remodelling proteins than sedentary individuals (Koves *et al.* 2013).

By using lipid infusions to increase circulatory FFA levels, Shepherd *et al.*, in this issue of *The Journal of Physiology*, elegantly examined the effect of lipid infusion on LD size, number and markers of LD dynamics in human skeletal muscle in a fibre type specific manner in trained and sedentary individuals (Shepherd *et al.* 2017). It was shown that lipid infusion augmented ectopic fat accumulation in type I muscle fibres in both trained and sedentary individuals. In the trained, the increase in ectopic fat was accounted for by an increase in number as well as in size of the LD (in type I and II fibres), whereas in sedentary individuals only the number of LDs increased (Shepherd *et al.* 2017). Interestingly, lipid infusion promoted a

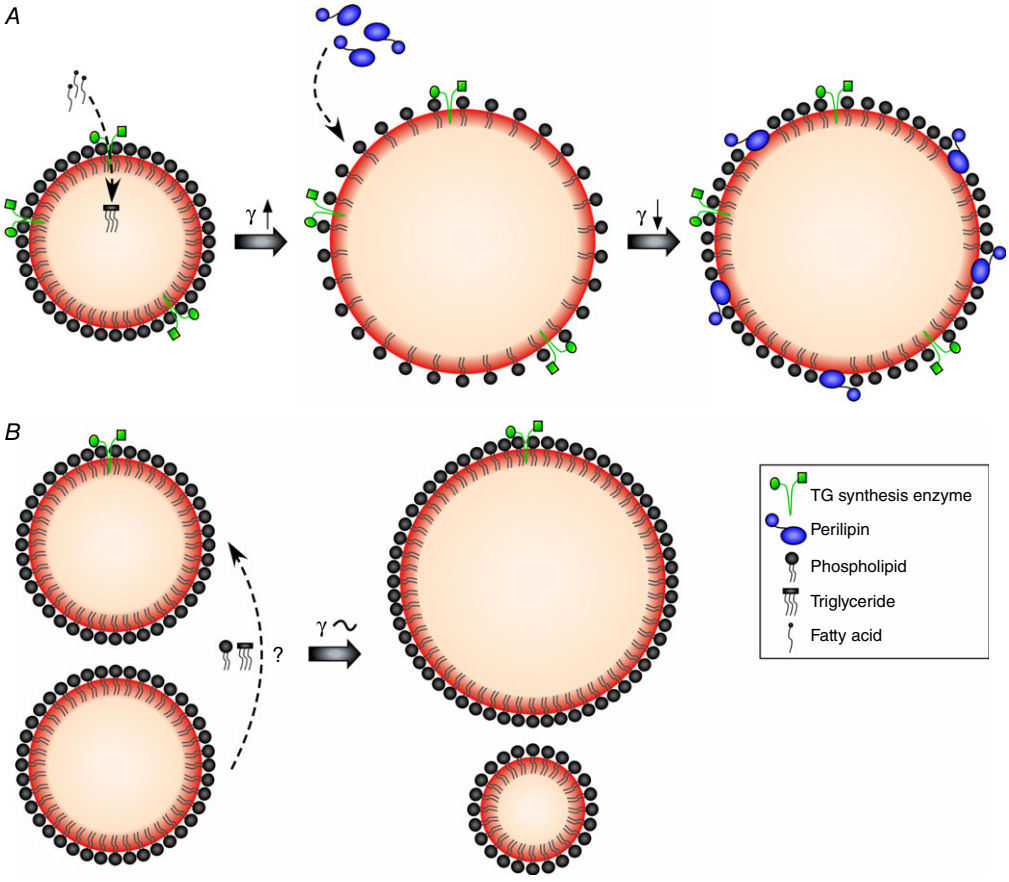

Figure 1. Hypothetical model of lipid droplet growth in trained versus sedentary subjects
A, in trained individuals, high availability of FFAs promotes TG synthesis and LD growth, leading to increased surface tension (γ), possibly recruiting perilipins to the phospholipid membrane. *B*, in sedentary individuals, LD growth may occur via ripening, rendering lipid droplets with low surface tension and no increased protein binding.

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redistribution of PLIN2, PLIN3 and PLIN5, resulting in a higher number of LDs decorated with PLINs. This was only observed in the trained individuals, the population also possessing LD size increments. By design, the present study does not permit conclusions as to whether the LDs in the trained increase in size as a consequence of augmented decoration with PLIN proteins, or whether the growth of the droplet facilitates binding/recruiting of PLIN proteins to the LD surface. It is, however, interesting to note that we previously observed that augmenting FFA availability to skeletal muscle upon prolonged fasting (a model of physiological insulin resistance) resulted in increased LD size and number and redistribution of PLIN5 in fit (but untrained) lean young individuals (Gemmink *et al.* 2016). Notably, in this population we showed that individuals who increased LD size most upon fasting were rendered least insulin resistant, which could be attributed to PLIN5 positive LDs. In addition, we had observed previously that trained individuals remain more insulin sensitive upon lipid infusion than sedentary individuals (Phielix *et al.* 2012). Jointly, these observations may indicate that having large LDs is not necessarily impeding muscle insulin sensitivity, provided that these LDs are decorated with PLIN proteins. Other studies, that did not take LD decoration into account, have shown negative correlations between LD size and insulin sensitivity (He *et al.* 2004). So, how to reconcile the data on LD size in relation to insulin sensitivity?

Various models for modulating LD size exist (Thiam *et al.* 2013). LDs can grow in size by ripening, during which molecules from one LD diffuse into another LD, resulting in an increased range in LD size as some LDs grow at the expense of others that reduce in size (Thiam *et al.* 2013), a phenomenon that may occur in sedentary individuals (Fig. 1*B*). Typically, ripening results in large LDs covered by a dense phospholipid monolayer with a low surface tension. Alternatively, LDs can expand by increased synthesis of TG from the increased availability of FFAs. This requires the abundant presence of lipogenic enzymes (which is typical to the trained state) and results in large LDs with more spacing between the phospholipid molecules making up the LD membrane (Fig. 1*A*). This increased spacing increases the surface tension of the large LD and permits the binding of proteins, as was observed in the present study for proteins of the PLIN family (and possibly for other proteins involved in LD dynamics). Moreover, large LDs with increased surface tension permit the sequestering of amphipathic molecules with recognized insulin desensitizing properties (like bioactive lipid moieties). This model of size growth is compatible with the observations made upon lipid infusion in the trained. Thus, this model of LD size growth provides an appealing explanation for the dual face of large LDs with respect to insulin sensitivity. Moreover, and particularly in the trained state with high fluctuations in metabolic demand, decoration of large LDs with PLIN proteins may serve to match the hydrolysis of triacylglycerol with mitochondrial fat oxidation. Specifically for PLIN5, the data seem to suggest that large LDs coated with PLIN5 also promote LD-mitochondrial tethering. The present paper, along with our hypothetical model, puts LD dynamics central stage for future research linking ectopic fat storage with insulin sensitivity and oscillations in fat oxidation. This underscores the importance of a more detailed examination of the players involved in LD dynamics.

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Additional information

Competing interests

None declared.