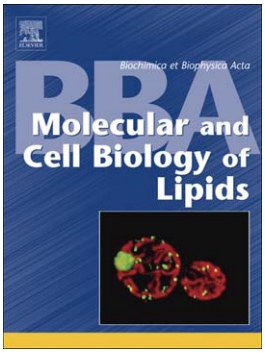

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PII: S1388-1981(17)30149-X
DOI: doi:10.1016/j.bbalip.2017.08.002
Reference: BBAMCB 58191

To appear in: *BBA - Molecular and Cell Biology of Lipids*

Please cite this article as: Rosalind A. Coleman, Matthijs Hesselink, Recent advances in Lipid Droplet Biology, *BBA - Molecular and Cell Biology of Lipids* (2017), doi:10.1016/j.bbalip.2017.08.002

Recent advances in Lipid Droplet Biology

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Since antiquity, the presence of excess adipose tissue has been identified as a cause of poor health and diminished longevity. Hippocrates wrote, “It is very injurious to health to take in more food than the constitution will bear, when, at the same time one uses no exercise to carry off this excess” [1]. Although similar ideas recorded through the centuries continued to expose the health hazards of obesity [2], our current understanding of why excess fat accumulation is injurious has required multiple technical advances. These include the ability to separate different forms of lipids, the development of histological techniques, the recognition that triacylglycerol (TAG) accumulation is associated with insulin resistance and the metabolic syndrome, the identification of enzymes of TAG synthesis and degradation, and finally, the realization that lipid droplets (LDs) are not just accumulations of inert lipid, but are, in fact, functional cellular organelles.

LDs were first noticed in cells in the 1880s when “lifeless food-matter” was described in egg yolk and egg cytosol as “fat-drops, “oil-drops,” or “fatty deutoplasm-spheres” [3] and in frog fatty liver [4]. After these initial histological descriptions, LDs were noted in a variety of tissues, including the adrenal gland in which they were believed to represent a “glandular product” [5]. In the 1950s and 60s, when intracellular structures could be visualized by electron microscopy, conflicting views arose as to the origin of LDs, including their possible derivation from microbodies that were also the source of mitochondria [6, 7] or their development in intracisternal spaces of the endoplasmic reticulum [8]. LDs were notable in regenerating liver after partial hepatectomy [9], where they were thought to be taken up by pinocytosis and perhaps then oxidized, since they seemed to associate with mitochondria [10]. Pinocytosis of tiny, unobservable LDs was also believed to occur in intestinal epithelial cells after a fatty meal [11]. It was recognized that the origin of LDs differed from that of lipoprotein particles because when isolated perfused livers were incubated with puromycin to block protein synthesis, only the production of lipid within the secretory apparatus was inhibited [12]. The fate of LDs was also a matter of contention. For example, it was considered likely that after cream feeding, tiny lipid droplets might enter intestinal mucosal cells, coalesce, and then reach the Golgi complex intact for secretion into the lymph [11, 13].

Meanwhile, biochemical studies determined the location of TAG synthesis. Autoradiography after injections of tritiated glucose indicated that TAG was synthesized in the endoplasmic reticulum of intestinal epithelial cells [14] and liver [8]. The endoplasmic reticulum location was confirmed by showing that, apart from phosphatidic phosphohydrolase, all the enzymes of TAG and phospholipid synthesis were present in liver microsomal fractions [15].

In spite of the fact that they were present in virtually every cell, little attention was paid to the LDs themselves, apart from recognition that their fatty acid content was a cellular source of energy and contributed to the synthesis of the TAG that was secreted in lipoproteins and milk. The origin of LDs was of little interest until the discovery in 1991 of the first droplet-specific protein, the heavily phosphorylated perilipin 1 (PLIN1) [16]. Since then, interest in LDs has