Lipid Droplets: emerging therapeutic targets for cancer treatment

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Background

Lipid Droplets (LD) are ubiquitous fat storage organelles that play relevant roles in lipid metabolism, cell signaling and production of inflammatory mediators. Although disregarded for decades, they have gained renewed interest in recent years, upon the description of increased numbers of LD in several tumors, placing them in the spotlight of **cancer research**[1].

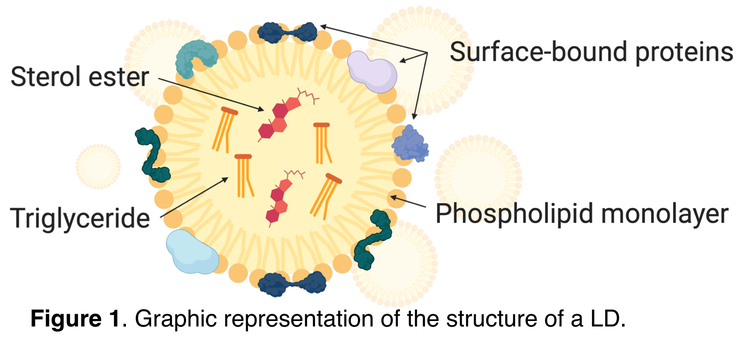

Figure 1. Graphic representation of the structure of a LD.

Aims

- ➤ To establish a conceptual framework to understand the roles of LD in tumor microenvironments.
- ➤ To revise the current knowledge about LD biogenesis and breakdown pathways.
- ➤ To explore the possibility of developing anticancer strategies based on the inhibition of LD-related proteins.

Methodology

Extensive literature review on the biology of LD (Nov 2019 – May 2020).

- **Databases**: MEDLINE, Web of Science, ScienceDirect.
- **Key words:** Lipid Droplet, Cancer, Cellular Stress, Metabolic Reprogramming.
- **Inclusion criteria**: original and review articles published after 2010, secondary sources.

LD in the harsh tumor microenvironment

LD biogenesis is induced by a range of **stress environmental factors** and cellular states, most of them representative of tumor microenvironments[1,2].

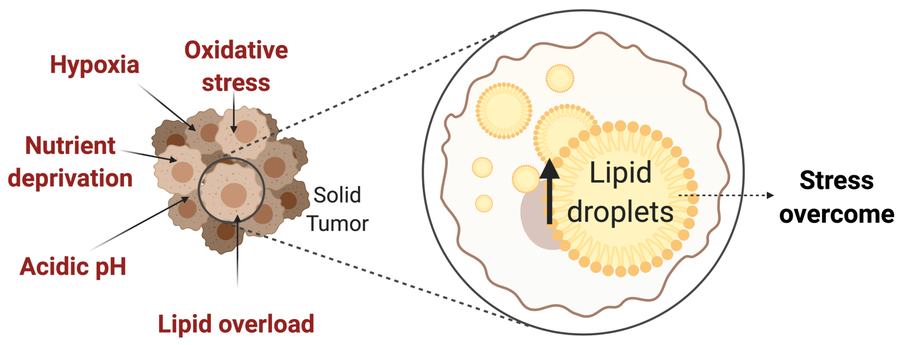

Figure 2. Stress conditions in the tumor microenvironment induce LD biogenesis. In these conditions, the accumulation of LD is associated to stress overcome.

LD are major regulators of lipid uptake, distribution and consumption, which are usually dysregulated in cancer cells[1-4].

However, further **roles** have been recently described, resulting in stress scavenge and cellular homeostasis maintenance[3].

As a result, LD contribute to **cell survival** and **tumor growth**.

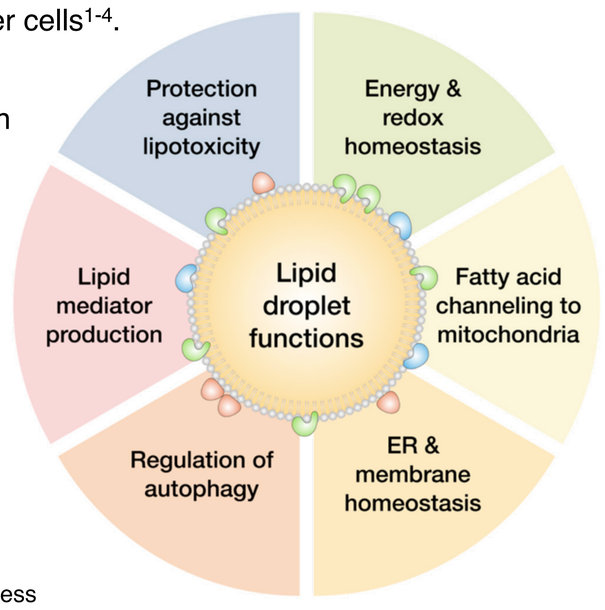

Figure 3. LD functions in cells under stress conditions. *Reprinted from: Lipid Droplets in Cancer: Guardians of Fat in a Stressful World by Petan T and Jarc E.*

Targeting LD metabolism

Research on LD biology currently aims to identify the **molecular pathways** underlying the prosurvivial roles. Several proteins have been identified, but the heterogeneity of cancer cells entails major obstacles[1-4].

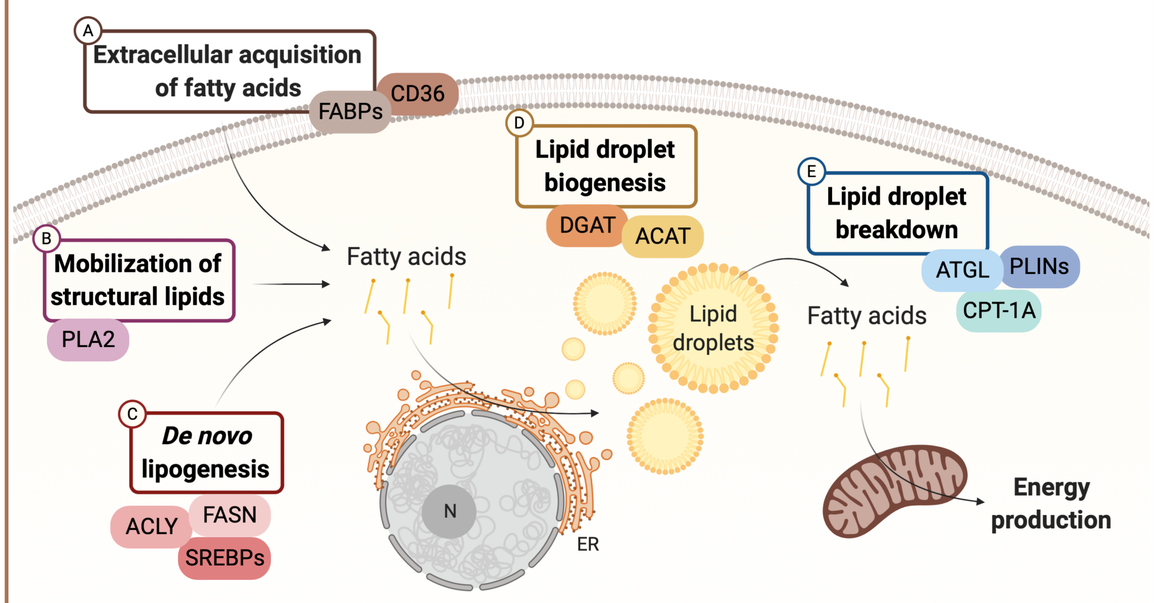

Figure 4. Essential molecular pathways for LD protective functions involve fatty acid acquisition (A-C), synthesis of LD in the ER (D) and LD catabolism (E). Color boxes show the most studied proteins of each pathway.

Despite the uncomplete knowledge, studies have shown that preventing the roles of the identified proteins could be used as an anticancer approach, since the reduction of LD levels translates into lowered cancer cell survival rates[4].

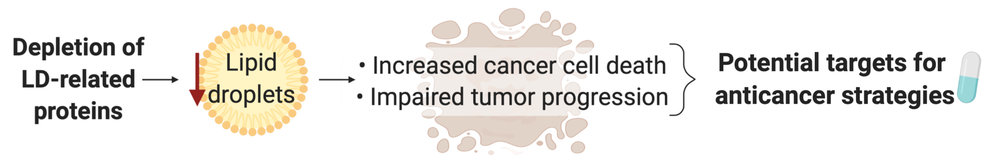

Figure 5. Depletion of proteins important in LD biology emerge as a strategy to treat cancer.

Current state of cancer therapies targeting LD

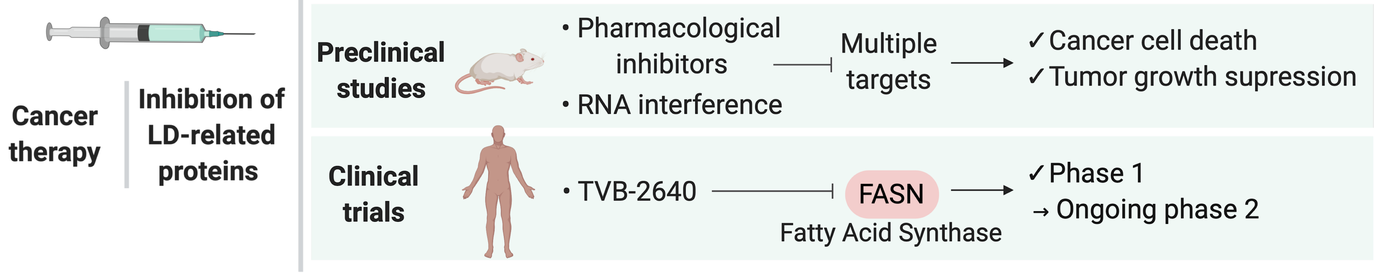

Figure 6. Overview of the current preclinical studies and clinical trials working on the development of LD inhibitors.

→ Inhibitors for most of the identified proteins are still being studied in **animal models**.

→ The fatty acid synthase (FASN) inhibitor **TVB-2640** is the only one being tested in cancer patients[4].

→ The results from both preclinical and clinical studies are promising, proving the **feasibility of targeting lipid metabolism** to stop cancer progression.

Concluding remarks

❖ Accumulation of LD in cancer cells has multiple **stress-scavenging effects**, which are essential for cell survival and proliferation in harsh microenvironments. However, the exact underlying mechanisms lack further elucidation.

❖ Many proteins involved in LD biogenesis and breakdown pathways have emerged as potential **targets for inhibition** in anticancer therapies, being **TVB-2640** the most promising and better studied drug at the moment.

❖ In order to perfect the developing therapies and to contribute to the incessant improvements in cancer treatments, **further research** on the abnormal lipid metabolism in cancer cells is fundamental.

References

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2. Olzmann JA, Carvalho P. Dynamics and functions of lipid droplets. *Nat Rev Mol Cell Biol*. 2019;20(3):137– 55.
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