

# Observation-driven inquiry: Raman spectroscopic imaging illuminates cancer lipid metabolism

Aurelio Lorico<sup>1</sup>, Germana Rappa<sup>1</sup>, Denis Corbeil<sup>2</sup>, Thuc T. Le<sup>3</sup>

<sup>1</sup>Department of Pathology, College of Medicine, Roseman University of Health Sciences, 10530 Discovery Drive, Las Vegas, NV 89135, USA;

<sup>2</sup>Biotechnology Center and DFG Research Center, Technische Universität Dresden, Tatzberg, Dresden, Germany; <sup>3</sup>Department of Biomedical Sciences, College of Medicine, Roseman University of Health Sciences, 10530 Discovery Drive, Las Vegas, NV 89135, USA

*Correspondence to:* Aurelio Lorico and Thuc T. Le. Roseman University of Health Sciences, 10530 Discovery Drive, Las Vegas, NV 89135, USA. Email: alorico@roseman.edu; tle5@roseman.edu.

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Metabolic reprogramming of cancer cells trades energy efficiency for biomass accumulation to support growth and proliferation (1). Indeed, cancer cells are known to have increased endogenous fatty acid synthesis, exogenous fatty acid uptake, and lipid droplet accumulation to support biosynthesis of membrane and signaling molecules (2). Targeting fatty acid biosynthesis has been shown to be an effective means to control cancer cell proliferation (3). Conjugation of drug molecules with lipids for enhanced tumor targeting is an ongoing strategy in drug delivery (4). In addition, intracellular lipid and cholesterol accumulation have been used as novel biomarkers for cancer aggressiveness (5), cancer stem cells (6), and circulating tumor cells (7). Together, lipid metabolism is emerging as an exploitable cellular process for cancer diagnosis and therapy.

Epitomizing the observation-driven scientific inquiry, Li *et al.* recently deployed a novel Raman spectroscopic imaging technique to uncover lipid unsaturation as a biomarker of ovarian cancer stem cells (CSCs) (8). Following this critical observation with carefully designed experiments, the authors identified a relationship between lipid desaturation, cancer stemness, and the NF- $\kappa$ B signaling pathway. They found that interference with lipid desaturation by small-molecule inhibitors of stearoyl-CoA desaturase 1 (SCD1) impaired cancer stemness, inactivated the NF- $\kappa$ B pathway and blocked the tumor initiation

capacity of ovarian CSCs. The authors proposed lipid desaturation as a novel target for CSC-specific therapy.

Interestingly, the findings by Li *et al.* reflect a convergence of scientific literature supporting the interaction of the cholesterol-binding, CSC-associated protein CD133 with lipid metabolism and cancer-related signaling pathways in carcinogenesis (9). For example, a direct correlation between the expression of CD133, Wnt/ $\beta$ -catenin signaling activity and intracellular lipid droplet accumulation was previously observed in melanoma (10) and colorectal CSCs (6). Accordingly, Li *et al.* found an increased amount of intracellular lipid droplets in ALDH<sup>+</sup>/CD133<sup>+</sup> ovarian CSCs compared to their ALDH<sup>-</sup>/CD133<sup>-</sup> ovarian non-CSC counterpart. On the other hand, the relationship between lipid desaturation and NF- $\kappa$ B signaling pathway found by Li *et al.* was consistent with known integration of metabolic regulation and immune response mediated by the toll-like receptor signaling pathways (11). The interaction with oncogenic signaling pathways supports lipid metabolism as a suitable target for anti-cancer therapy.

Furthermore, multiple earlier publications reported the universal effectiveness of SCD1 inhibition in limiting the growth of cancer cells of various origins including lung, breast, prostate, and colon (12,13). Most significant was the observation that SCD1 and lipid desaturation were required for the formation and growth of cancer spheroids or xenograft tumors (8,12). This observation supports the

theory of re-activation of *de novo* lipogenesis in solid tumors as part of cancer metabolic reprogramming. Since most tissues utilize dietary lipids, targeting *de novo* lipogenesis and lipid desaturation could provide a selective mechanism to interfere with tumor growth. Furthermore, SCD1 could be a therapeutic target for a broad range of cancer types, as SCD1 expression is also increased in liver, kidney, and esophageal tumors.

However, clinical utilization of SCD1 inhibitors for anti-cancer therapy should proceed with extreme caution. Considering the established link between obesity and risk of many types of cancer, the observation that SCD1 deficiency protected mice against high-fat diet-induced obesity and hepatic steatosis (13) suggests that SCD1 inhibitors could serve the dual purpose of blunting tumor growth and preventing obesity and associated metabolic conditions. On the other hand, loss of SCD1 function has been associated with the development of skin alopecia and inflammation, pancreatic  $\beta$ -cell dysfunction, liver dysfunction, and atherosclerosis (13). Furthermore, SCD1 is highly expressed in the brain. Small-molecule inhibitors of SCD1 could cross the blood-brain barrier and interfere with the axon myelination process. Therefore, therapeutic strategies that target the re-activation of *de novo* lipogenesis of tumor tissues should take into consideration the risks of interference with active *de novo* lipogenesis in normal tissues.

The utilization of hyperspectral stimulated Raman scattering (SRS) microscopy by Li *et al.* sets this study apart from others in this emerging field of cancer lipid metabolism. Hyperspectral SRS microscopy is a fast, non-invasive, and label-free chemical imaging technique that can visualize the distribution of lipid droplets, cholesterol, and proteins in single cells. Compared to spontaneous Raman microscopy, previously employed by Tirinato *et al.* to visualize lipid droplets in colorectal CSCs (6), hyperspectral SRS microscopy is at least 25,000 times faster. To put this time scale in perspective, a 512 pixels  $\times$  512 pixels image could be acquired in less than 1 minute with hyperspectral SRS microscopy versus approximately 364 hours with spontaneous Raman microscopy using reported pixel dwell time of 200 microseconds and 5 seconds, respectively (6,8). Furthermore, single-spectrum SRS imaging has achieved video rate of 20 frames per second. Fast image acquisition time scale renders SRS microscopy suitable for the studies of lipid metabolism in living biological systems (14). Indeed, SRS microscopy has been used to visualize various aspects of lipid metabolism, including fatty acid and glucose uptake, *de novo* lipogenesis, lipid desaturation, and cholesterol

uptake and storage in living cells. Future applications of SRS technologies could include the detection of CSCs and circulating tumor cells with intravital imaging and flow cytometry methods.

Lastly, the novelty of the study by Li *et al.* lies in the possibility of using specific types of lipids as biomarkers for cancer subtypes. Traditionally, protein expression levels serve as biomarkers to distinguish cancer subtypes. However, immuno-labeling methods to detect protein expression often require tissue fixation, which prevents the recovery of live cells for further studies. Moreover, intrinsic autofluorescent molecules such as retinol, riboflavin, flavin, lipofuscin, and melanin interfere with the detection of fluorescently conjugated antibodies. In contrast, Li *et al.* identified ovarian CSCs non-invasively and in a label-free manner by probing the intrinsic carbon-carbon double bonds of the lipid chains. Future usage of Raman tags such as isotopic  $^2\text{H}$ - or  $^{13}\text{C}$ -labeled or alkyne-tagged lipids, glucose, cholesterol, and other biomolecules will expand the capability of Raman spectroscopic imaging to assess metabolic differences between cancer subtypes for diagnosis and identification of therapeutic targets.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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