DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

41° Cycle

Title of the research: Exploring extracellular lipid droplets from lipid-storing cells as a novel mechanism of cell-to-cell communication

Supervisor: Prof. Luciana DINI; luciana.dini@uniroma1.it

Co-supervisor: Dr. Stefano TACCONI; stefano.tacconi@uniroma1.it

Summary (max 500 words):
Lipid-based particles play a crucial role in cell communication and the maintenance of physiological balance. Among these, extracellular vesicles (EVs) have been extensively studied as key mediators of intercellular signalling (1). These membrane-bound particles transfer lipids, proteins and genetic material between cells, thereby influencing various physiological and pathological processes (1,2). However, less attention has been paid to lipid droplets (LDs), which share structural and compositional similarities with EVs and are involved in the storage of neutral lipids within cells (3). LDs are composed of a neutral lipid core, consisting mainly of triglycerides (TAGs) and sterol esters, encapsulated by a monolayer of phospholipids. As dynamic and well-consolidated organelles, LDs play a key role in intracellular communication and are involved in complex interactions with key cellular structures such as the endoplasmic reticulum, mitochondria and lysosome (3,4). Through these interactions, LDs play a critical role in regulating lipid metabolism, maintaining energy balance and coordinating cellular responses to stress (4). Perturbations in LD biology have been linked to several metabolic disorders, including obesity and its associated changes (4). While traditionally associated with lipid-storing cells such as adipocytes, recent evidence suggests that LDs may also be released extracellularly and involved in cell communication, particularly in metabolic disorders such as obesity (5-7). In obesity, the increase in size and number of LDs in adipose tissue is a major contributor to chronic inflammation and associated metabolic disorders (2). In this context, recent research has uncovered a unique subset of adipose tissue macrophages, known as TREM2+/lipid-associated macrophages (LAMs), that form a crown-like structure around hypertrophic adipocyte. These LAM macrophages are involved in lipid storage within LDs, which appears to play a protective role by preventing excessive tissue expansion and alleviating metabolic problems associated with obesity (8). Our preliminary data indicate that exposure of THP1-derived macrophages to fatty acid overload induces a phenotypic shift towards a TREM2+/LAM-like state, accompanied by significant changes in LD dynamics and the release of a heterogeneous population of vesicles, including large extracellular LDs. Notably, the secretion of these LDs appears to be associated with the clustering of CD81 at the plasma membrane, a well-known tetraspanin involved in EV trafficking and secretion, suggesting a potential overlap in the release mechanisms between EVs and LDs. Based on these preliminary data and current knowledge, this PhD project aims to: (i) characterise the mechanisms underlying the secretion of LDs from lipid-storing cells, (ii) explore the role of extracellular LDs in intercellular communication, (iii) investigate the interaction between LDs and EVs in lipid transfer and cell signalling, and (iv) investigate how LD dynamics contribute to obesity-related metabolic disorders.

Pertinent Publications of the proponent (last 5 years):

- Moliterni C, Vari F, Schifano E, Tacconi S, Stanca E, Friuli M, Longo S, Conte M, Salvioli S, Gnocchi D, Mazzocca A, Uccelletti D, Vergara D, Dini L, Giudetti AM. *Lipotoxicity of palmitic acid is associated with DGAT1 downregulation and abolished by PPARα activation in liver cells*. J Lipid Res. 2024 Dec;65(12):100692. doi: 10.1016/j.jlr.2024.100692. Epub 2024 Nov 5. PMID: 39505261; PMCID: PMC11648247.
- Manganelli V, Dini L, Tacconi S, Dinarelli S, Capozzi A, Riitano G, Recalchi S, Caglar TR, Fratini F, Misasi R, Sorice M, Garofalo T. *Autophagy Promotes Enrichment of Raft Components within*

Extracellular Vesicles Secreted by Human 2FTGH Cells. Int J Mol Sci. 2024 Jun 4;25(11):6175. doi: 10.3390/ijms25116175. PMID: 38892363; PMCID: PMC11172899.

- Tacconi S, Vari F, Sbarigia C, Vardanyan D, Longo S, Mura F, Angilè F, Jalabert A, Blangero F, Eljaafari A, Canaple L, Vergara D, Fanizzi FP, Rossi M, Da Silva CC, Errazuriz-Cerda E, Cassin C, Nieuwland R, Giudetti AM, Rome S, Dini L. *M1-derived extracellular vesicles polarize recipient macrophages into M2-like macrophages and alter skeletal muscle homeostasis in a hyper-glucose environment*. Cell Commun Signal. 2024 Mar 27;22(1):193. doi: 10.1186/s12964-024-01560-7. PMID: 38539237; PMCID: PMC10967050.
- Rome S, Tacconi S. High-fat diets: *You are what you eat….your extracellular vesicles too!* J Extracell Vesicles. 2024 Jan;13(1):e12382. doi: 10.1002/jev2.12382. PMID: 38151475; PMCID: PMC10752826.
- Sbarigia C, Tacconi S, Mura F, Rossi M, Dinarelli S, Dini L. *High-resolution atomic force microscopy as a tool for topographical mapping of surface budding*. Front Cell Dev Biol. 2022 Oct 12;10:975919. doi: 10.3389/fcell.2022.975919. PMID: 36313576; PMCID: PMC9597496.
- Dini L, Tacconi S, Carata E, Tata AM, Vergallo C, Panzarini E. *Microvesicles and exosomes in metabolic diseases and inflammation.* Cytokine Growth Factor Rev. 2020 Feb;51:27-39. doi: 10.1016/j.cytogfr.2019.12.008. Epub 2020 Jan 3. PMID: 31917095.