The escalated incidence of metabolic diseases, including insulin resistance and type 2 diabetes (T2D), calls for a better understanding of the mechanisms underpinning these disorders. Being crucial in the regulation of whole-body energy homeostasis, the dysfunction of subcutaneous adipose tissue (SAT) is central to the development of metabolic diseases and the progression of comorbidities, including cancer (1).

In this context, our research activity has been focused on: 1. the molecular basis of a higher susceptibility to T2D; 2. the mechanisms underlining the association between altered metabolic conditions and breast cancer progression.

1. The central hypothesis of the first purpose predicts that risk of T2D is largely determined by epigenetic modifications occurring in response to environmental hits (2, 3). This hypothesis complement information accumulated through the past 20 years revealing the marginal role of genetics on T2D risk and the major impact of environment – lifestyle in particular – on diabetes onset. We have been focusing on T2D risk in humans. We have investigated both first degree relatives (FDR) of individuals with T2D and obese individuals as both of these groups have high risk of developing diabetes. Genome-wide studies in FDR individuals led to the generation of a human dataset including detailed information on the epigenetic profile specific of these subjects, as compared to individuals who are not FDR. Out of these data set, we have been investigating epigenetic variation affecting mitochondrial biogenesis (TFAM locus), senescence (ZMAT locus), human and mouse adipogenesis (HOXA5 locus), neurodegenerative disorders (ADRA2 locus) as well as three specific miRNAs targeting the IGF2 gene. Studies in obese humans have been so far focusing on the ANKRD26 gene and its impact to cardiometabolic risk (4). A population of severely obese subjects with either normal or impaired glucose tolerance or T2D (with non-obese normotolerant) subjects suitable for epigenetic studies has been further recruited before and 1 yr. after bariatric surgery. Detailed clinical information from these subjects has been collected. We are now exploring genes whose epigenetic profile associate to obesity and is reverted by bariatric surgery.

2. The aim to define the molecular players in the association between metabolic conditions and breast cancer (BC) progression is sustained by the hypothesis that alterations of adipose tissue function contribute to worsen cancer phenotype, affecting both prognosis and treatment of the neoplastic patient (5). Major findings obtained so far by our research activity show that: 1. Adipocyte-released insulin-like growth factor-1 is regulated by glucose and fatty acids and controls BC cell growth in vitro (6); 2. Adipose microenvironment promotes triple negative BC cell invasiveness and dissemination in high glucose concentrations, by producing CCL5 chemokine; peritumoral expression of CCL5 correlates with lymph node and distant metastasis in patients (7); 3. Glucose impairs tamoxifen responsiveness modulating Connective Tissue Growth Factor (CTGF) in BC cells and Interleukin-8 in adipose tissue; CTGF expression in tumoral tissue correlates with endocrine resistance in patients with BC (8).

Ongoing studies indicate that glucose modifies the complex relationship between BC cancer cells and mammary mesenchymal stem cells (MSCs) contributing to loss of multipotency and acquisition of fibroblast-like and senescence features in MSCs (CAF-cancer associated fibroblasts), besides the acquisition of a more aggressive phenotype in BC cells.
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Parole chiave:
Cancer; Diabetes; Epigenetics.

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