**Title:** Connecting DNA repair and metabolic alterations of obesity in a search for predictive

biomarkers **Principal Investigator:** Eugenia Dogliotti

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**Abstract:**

Obesity is a high prevalence multifactorial disease with major comorbidities. The rapid increase of obesity incidence in the population with minimal genetic flux underlines the importance of environmental factors in the pathogenesis of obesity and its metabolic complications. While lifestyle-related obesity risk factors are known, the underlying molecular pathways await clarification. Our working hypothesis is that increased production of metabolic byproducts (e.g. ROS or lipid peroxides) generated by chronic excessive caloric intake, causes persistent DNA damage and chronic DNA damage response (DDR) leading to local and systemic chronic inflammation followed by metabolic derangement. To identify differently regulated molecular pathways in obese versus lean individuals we plan to study two different models: a) body mass index (BMI) discordant monozygotic (MZ) twins before and after diet-induced weight loss to determine which pathways are modulated independently of inherited genetic factors, and b) massively obese patients before and after bariatric surgery to verify whether and how these pathways correlate with metabolic dysfunction. To this end we will use a wide range of advanced techniques such as metabolomics, lipidomics, inflammatory secretomics and DDR-targeted phosphoproteomics. Fat biopsies in severely obese patients will allow to address the critical issue of the relevance of the surrogate tissue for pathway analysis.

**Selected publications:**

-Rodier et al. (2009) Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. Nature Cell Biol. 11:973-979

-Karakasilioti et al. (2013) DNA damage triggers a chronic autoinflammatory response, leading to fat depletion in NER progeria. Cell Metab. 18:403-415

-[Shimizu I](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shimizu%20I%5BAuthor%5D&cauthor=true&cauthor_uid=25456739) et al. (2014) DNA damage response and metabolic disease. [Cell Metab.](https://www.ncbi.nlm.nih.gov/pubmed/25456739) 20:967-77

-Wiley et al. (2016) [Mitochondrial dysfunction induces senescence with a distinct secretory phenotype.](https://www.ncbi.nlm.nih.gov/pubmed/26686024) Cell Metab. 23:303-14