Energy metabolism and fertility as an essential balance for health in females

S. Della Torre[1,2], F. Lolli[1,2], R. Fontana[1,3], N. Mitro[1], M. Gomaraschi[1], E. Favari[4], C. Recordati[5], C. Meda[1,2], C. Ohlsson[6], M. Crestani[1], L. Calabresi[1], A. Maggi[1,2]

[1]Dept. of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy
[2]Center of Excellence for Neurodegenerative Diseases, University of Milan, Milan, Italy
[3]Dept. of Drug Discovery and Development, Italian Institute of Technology, Genova, Italy
[4]Dept. of Pharmacy, University of Parma, Parma, Italy
[5]Mouse and Animal Pathology Laboratory, Fondazione Filarete, Milano, Italy
[6]Centre for Bone and Arthritis Research, University of Gothenburg, Gothenburg, Sweden

In the liver, estrogens regulate energy homeostasis and lipid metabolism by activating the estrogen receptorα (ERα), the only isoform present in this organ. Pre-clinical and clinical studies suggest that this regulatory activity is sex-specific (Della Torre, 2014). Indeed, non-alcoholic fatty liver disease (NAFLD) and their consequent cardiovascular diseases (CVDs) are more common in men than in pre-menopausal women and after menopause the lack of estrogen signaling is associated with an incidence of NAFLD and CVDs comparable to men. To date, the mechanisms underpinning these liver specific protective effects of estrogens remain unclear due to a lack of appropriate model systems. To elucidate the physiology of estrogen action in the liver, we selectively deleted the hepatic ERα gene by the use of the cre-lox technology (Della Torre, 2011). These mutants, named LERKO, show a regular reproductive cycle and therefore enable the study of the role of liver ERα in the context of female reproductive physiology. The studies carried out so far point to liver ERα as a key regulator of cholesterol homeostasis and led us to propose this receptor as the target for the treatment of the metabolic disorders associated with the post-menopause (Della Torre et. al, *submitted*).
The aim of the present study was to investigate the role of hepatic ERα in the control of lipid metabolism in females fed with a regular diet or challenged with a diet enriched in fat (60% high-fat diet, HFD).
The study shows that the hepatic ERα is essential for the synthesis of a class of HDL characterized by small size, high triglycerides and low protein content, and an increased ability to induce macrophage cholesterol efflux. The synthesis of these specific HDL occurs during proestrus, when the circulating levels of estradiol are highest, but not in the course of the other phases of the estrous cycle. We propose that these HDL are essential for the elimination of the excess of lipids accumulated during the progression of the reproductive cycle culminating with the ovulation. The exposure to HFD demonstrates that the hepatic ERα acts as a sensor able to adapt the lipid metabolism and the inflammatory response to nutritional changes. At more molecular level, we demonstrate that the activity of hepatic ERα on cholesterol metabolism is mediated by the cross-talk with liver x receptor α (LXRα).
The study provides the bases for a novel understanding of estrogen protective effects against metabolic and cardiovascular diseases and unravels the pivotal role of hepatic ERα in coordinating the metabolic flexibility in the female liver in response to nutritional changes.
All these results could be potentially relevant for the design of innovative HRTs that can restore the positive effects exerted by estrogens in the fertile age and that are lost in women with aging.

Della Torre et al. (2014). *Nat Rev Endocrinol*. 10, 13-23.
Della Torre et al. (2011). *Cell Metabolism*. 13, 205-14.