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Titolo	FUNCTIONAL ROLE OF ESTROGEN RECEPTORS DURING AGING AND THEIR INVOLVEMENT IN INFLAMMATORY PROCESSESS [Tesi di dottorato]
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Sommario	Estrogens are female sex hormones, belonging to a group of steroids, and they are responsible for the sexual characteristics of the female. They also have effects on bone, cardiovascular system, brain, and skin. The effects of estrogens are mediated by binding to their cognate receptors, the estrogen receptors (ER? and ER?). ERs are transcription factors that regulate transcription by associating with estrogen-responsive-elements (EREs) located within the promoter of target genes. The aim of my studies was to evaluate the effect of aging and blockade of ovarian functions on estrogen receptor transcriptional activity and ER anti-inflammatory action . In specific aim #1 we proposed to study genes driven by ERE-containing promoters: endogenous as well as surrogate reporters; within specific aim #2 we proposed to provide support to the theory that lack of estrogen anti-inflammatory activity is a major component for the onset of pathologies associated with menopause (osteoporosis, atherosclerosis, metabolic and neurological dysfunctions). In our study we evaluated ER activity during aging in ERE-Luc mice. The analysis showed that ER? is still synthesized during while with age, ovariectomy further increases ER? content in uterus, aorta and hippocampus, but not in the brain. To evaluate ER transcriptional activity in aging and after ovx we first studied the expression of the reporter luciferase (by measuring luciferase

	mRNA); next we evaluated the expression of ER endogenous genes such as Prothymosin alpha (PTMA) and Progesteron Receptor (PgR) known to be a direct target of ER. This study showed that the ER present in aged tissues is fully functional from the transcriptional point of view. In ovx animals the trend of ER activity is unclear. We were intrigued by the observation that, in aged female mice, a reduction of circulating levels of estrogens induced by ovariectomy was associated with an increased ER activity in several organs. To further study this phenomenon we gonadectomised male and female mice at the age of 5 months and we measured luciferase activity by in vivo imaging at 6 or 20 months of age. Luciferase activity is higher in females than in males in both groups of age, however gonadectomy does not affect luciferase activity in young males (with the exception of the chest), but clearly decreases photon emission in aged mice. In our study we also tested the hypothesis that with aging the loss of the anti-inflammatory activity of estrogens may explain the increased susceptibility to inflammatory disorders (i.e., osteoporosis, atherosclerosis, diabetes, certain neurodegenerative disorders), reported by epidemiological studies in women. Our analysis focused primarily on TNF?, IL1?, MCP1 and MIP2. The mRNA of all these inflammatory mediators was shown to increase progressively with aging. To evaluate the influence of estrogens on the expression of inflammatory genes, we measured the content of mRNA encoding for inflammatory mediators in different tissues of ovariectomized females. Due to the relevance of inflammatory processes in the CNS, we next focused on the effect of ovariectomy in the different brain areas by IHC studies the state of reactivity of microglia and astrocytes, cells known to play a relevant role in neuroinflammation. Our data show morphological differences between astrocytes in ovariectomized compared to sham operated mice in all the brain areas at all months of age. Also microglia presents a morphological activation in all the brain areas, as observed in astrocytes. Finally we investigated the extent to which the susceptibility to an inflammatory stimulus changed during aging and if the ovariectomy was playing a role in this phenomenon. In the hippocampus TNF? production increases with aging, MIP2 and MCP1 espression changes at 12 months and is similar at 18 months, whereas mRNA levels of IL1 beta are not affected by aging. Ovariectomy does not seem to influence the inflammatory process.
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