## Molecular imaging to study hormone-induced cancers

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Cancer incidence is projected to increment further due to several causes, including the increased ageing of population. Sex-hormones play a role in the etiology of several cancer types including breast, ovarian, endometrial and prostate tumors. Breast and prostate neoplasias are respectively the first and second leading causes of cancer death in women and men and their incidence increases with ageing. Novel strategies for prevention are therefore needed to lower the social and economic impact of these diseases.

While the role of sex-hormones and their cognate receptors in the promotion of these malignancies has been fully investigated, little is known about the timing at which the signaling of these receptors is required for neoplastic transformation: drugs targeting these receptors are very efficiently preventing tumor formation (chemopreventive action) suggesting a role for their cognate hormones in the initial promotion of tumor growth, however the same drugs efficiently counteract metastatic cancers highlighting a relevant role for hormone signaling also at the final stage of tumorigenesis.

The working hypothesis of our study is that the precise identification of the initial tumorigenesis steps at which the receptor signaling is activated will allow the identification of significant events in the mechanisms underlying the initial tissue transformation of endocrine cancers. To identify these steps, we have investigated the dynamic of estrogen receptor (ER) activation during carcinogenesis by molecular imaging in a model of sporadic breast cancer in mice.

Our data provide evidence that ER activation is not constant during neoplastic transformation: indeed, we demonstrate the existence of an intermittent activation/inactivation switch of ER signaling occurring in waves with an average period of 4-6 weeks in animals that lately develop a breast tumor. One wave of activation occurs early, 8-14 weeks before the onset of a palpable, clinically evident tumor suggesting that an important change in the breast is occurring at this stage. The histopathological analysis of these tissues reveals the presence of a mammary intraepithelial neoplasia (MIN) resembling the human ductal carcinoma *in situ* (DCIS): proliferating cells are confined within ducts and lobules, do not have yet acquired the ability to invade the surrounding stroma and the tissue is characterized by a variable histiocyte infiltration with an increased expression of chemokines/cytokines. To gain insights in the signaling pathways modulated during this transition phase leading from an *in situ* to an invasive cancer, we have carried out a transcriptomic analysis on normal and MIN mammary glands. The results of this analysis: i) provide a clear view on the signaling pathways involved at this stage, ii) identify key nodal points that could be useful therapeutic targets for chemoprevention and iii) characterize a gene expression signature recognizing the pre-neoplastic tissue when compared to the normal mammary tissue; interestingly, this signature is well conserved also in humans hyperplasia, constituting a potentially clinically valuable set of markers for the prognosis of human DCIS.

*Aknowledgments*: This study was supported by Italian Association for Cancer Research (AIRC) IG-2011 n. 11903 and by Fondazione CARIPLO project n. 2009-2439.