In vivo imaging of ER activation reveals an inflammatory switch as a common early pro-carcinogenesis step in breast tumorigenesis

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Activation of the estrogen receptor (ER) is a well recognized key event in the process of mammary tumorigenesis, however, little is known about the timing when the receptor is activated during neoplastic transformation. In this study, we have investigated the dynamic of ER activation by in vivo imaging of the receptor activity during the entire carcinogenesis process in the ERE-Luc reporter mouse (Ciana et al., 2003): in this transgenic model, photon emission is a reliable measure of the receptor activation, thus, it is possible to non-invasively quantify the state of receptor activation in the mammary gland of the same mouse in time by taking a picture with a CCD-camera; this imaging procedure allows also to localize and determine the receptor activity at the same time. Breast cancer was induced by treating a group of 20 reporter mice with medroxiprogesterone acetate (MPA) and dimethylbenzanthracene (DMBA) according to a well established protocol of chemical carcinogenesis (Aldaz et al., 1996): this protocol induces adenocarcinoma of the breast in 60% of the mice, while 40% of the animals do not develop cancer. From the beginning of the treatment, animals were subjected weekly to a bioluminescence imaging session until tumor appearance. Retrospective data analysis of the dynamic of ER activation revealed the existence of waves of ER activation occurring in mice developing breast cancer. These cyclic activation correlates with the induction of immunity response as demonstrated with a similar in vivo imaging experiment carried out in another mouse model reporting the innate response. In particular, we found an early wave of activation occurring 8-14 weeks before the appearance of a palpable tumor which is correlating with the increased expression of several inflammatory markers in the breast tissue and the accumulation of TRAIL positive immune cells in lymph nodes. We provide evidence that ER activation occurs through an hormone-independent mechanism initiated by chemokine/cytokine signaling. We investigated the receptor activation in the breast tissue occurring during this early stage by RNA CHIP-SEQ analysis; transcriptomic highlight the existence of a specific modulation of energetic metabolism and inflammatory pathways during progression from this early stage of disease to the invasive cancer.

Ciana et al. (2003). Nature Medicine 9(1):82-6
Aldaz et al. (1996). Carcinogenesis 17(9):2069-72