IN7

REGULATION OF SELF-RENEWAL IN BREAST STEM CELLS

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Signaling receptors are internalized following their engagement by cognate ligands, in a process that has been traditionally considered crucial for long-term attenuation of receptor signaling. However, recent evidence has pointed also to an important role of endocytosis in conferring spatial and temporal dimensions to signaling (the signaling endosome concept). It is thus predicted that subversion of the endocytic machinery might play an important role in cancer. Of particular interest, in this contention, is an endocytic protein called Numb. Numb is a cell fate determinant that by asymmetrically partitioning at mitosis controls binary cell fate decisions. In human breast and lung cancers, there is frequent loss of Numb expression. This causes alterations in two major downstream pathways. On the one hand, lack of Numb allows for unchecked signaling activity of the Notch receptor. On the other, lack of Numb causes attenuation of the p53 signaling pathway. Tumors cells displaying loss-of-Numb expression are addicted to this event and to its molecular consequences. Our recent results point to the mammary stem cell (MSC) compartment as the cellular "target" of Numb misregulation in breast tumors. We have developed a technology to cultivate and purify mammary stem cells. In normal MSC, Numb is asymmetrically partitioned at mitosis. This in turn dictates the replicative fate, in that the Numb(+) cell remains quiescent (and retains MSC capabilities), whereas the Numb(-) cell acquires a progenitor fate and undergoes rapid symmetric divisions. The control of Numb over MSC fate is executed through the ability of Numb of silencing Notch signaling and maintaining high levels of p53 in the MSC. Lack of Numb in tumor MSC causes a switch form the asymmetric to the symmetric mode of division, thus forcing both daughter cells to assume the same replicative fate. Our understanding of how Numb is mechanistically involved in all these aspects will be discussed.

IN8

ROLE OF PATHOLOGY IN THE MANAGEMENT OF ADVANCED BREAST CANCER

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The first and most obvious role of the pathologist in the management of advanced breast cancer is to ascertain the actual nature of lesions suspected to be metastases of breast cancer. Some of these lesions may be nonneoplastic, or second primaries or metastasis from (unknown) cancers of different organs. If the tumors are negative for estrogen (ER) and progesterone receptors (PgR) it may be very difficult to prove or reject the hypothesis of a metastasis of breast cancer. In such circumstances it may be very helpful to use adjunct diagnostic tools, like the immunohistochemical markers of a pulmonary (TTF-1) or intestinal (CDX2) origin of the neoplasm.

If the mammary origin of the metastases has been confirmed, then the pathologist has a major role in informing the choice of the systemic treatment by ensuring the most accurate assessment of ER, PgR and HER2 status. The vast majority of breast cancer metastases retain the same biological features of the primary tumors, but changes in one or more of these parameters have been reported in up to 30% of the cases. It is still a matter of debate whether all these discordant cases are actually due to biological reasons, like the selection of tumor clones with different phenotypes, or they are at least in part due to technical artifacts. Furthermore, it has been documented that hormone receptor and HER2 status may differ in different metastases of the same primary tumors, raising the question whether it is clinically useful to biopsy the metastases whenever feasible. The biopsy of the metastatic site may be justified when there is uncertainty about the nature of the lesion, or the disease has run an unexpected clinical course. Also, in case of a primary tumor with the triple-negative phenotype, it may be worth considering a biopsy of the metastasis to ascertain whether the metastatic tumor now expresses ER or HER2, thus making the patient eligible for a targeted treatment.

IN9

OVERVIEW OF IMAGING TESTS FOR ASSESSMENT OF METASTASES IN BREAST CANCER

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Various imaging tests, including hybrid and whole-body technologies, are available for assessment of metastases in women affected by breast cancer. Imaging for detection or investigation of metastases (or suspected metastases) in breast cancer can be applied in various settings with various purposes: at initial diagnosis of breast cancer (baseline staging) or at subsequent local relapse and/or suspected distant relapse (restaging); as part of surveillance in women with a history of early-stage disease; for investigation of symptoms raising suspicion of metastatic spread; and for monitoring response to therapy in established metastatic disease.

Evidence on imaging metastases in breast cancer will be presented, including two systematic reviews. For background, the presentation will briefly consider:

Current recommendations for imaging suspected metastases

Evidence from randomized trials comparing follow-up of women in early-stage breast cancer using routine surveillance (clinical examination and annual mammography alone) versus intensive surveillance that includes frequent clinical examination plus imaging for metastases (CXR, bone scan, liver US)

The focus of the presentation will be the results of two *systematic reviews* conducted to support the development of consensus recommendations at ABC1:

Systematic evidence review, including quality appraisal, of studies reporting on *comparative* imaging accuracy for detection of *bone metastases* from breast cancer[1]. Initial results from this review, based on 16 relevant studies, showed heterogeneity across studies in the underlying prevalence of bone metastases (median 34%), and also in the quality of the applied reference standards. Studies generally compared newer imaging modalities to bone scan (BS) in subjects selected to have both BS and additional imaging. There was some evidence that PET, and very limited evidence that PET/CT, CT, and MRI, may provide small *increments* in accuracy relative to BS when used as *add-on* tests. Data on the accuracy of SPECT and whole-body MRI were very limited. There was little evidence to support the application of these imaging tests as a *replacement* to BS in initial imaging of suspected bone metastases

Evidence from observational studies of imaging tests for detection of *asymptomatic* metastases from breast cancer (review in progress)

1. N. Houssami, CM. Costelloe. Imaging bone metastases in breast cancer: Evidence on comparative test accuracy. *Annals of Oncology* 2011 (in press)

IN10

STATE-OF-THE-ART MANAGEMENT OF HER-2+ DISEASE

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HER-2 positive metastatic breast cancer (MBC) was once considered one of the most aggressive sub-types of this disease. With the development of efficacious targeted agents against the HER-2 receptor, the prognosis of this BC sub-type was substantially changed. Nowadays, patients with HER-2 positive MBC treated and responsive to anti-HER2 therapies have a better outcome than many patients with HER-2 negative disease.

The oldest drug in this setting is trastuzumab, a monoclonal antibody against the extra-cellular domain of the HER-2 receptor. Trastuzumab is