J Clin Exp Pathol 2018, Volume 8
DOI: 10.4172/2161-0681-C5-058



# Loss of numb in breast carcinogenesis: A paradigm for a mechanism-based selective anti-cancer stem cell therapy

**Daniela Tosoni**
European Institute of Oncology, Italy

The cell fate determinant Numb is a tumor suppressor in the mammary gland whose loss in human breast cancers results in p53 inactivation and an aggressive disease course. Numb-p53 downregulation leads to aberrant mammary morphogenesis and the emergence of cancer stem cells (CSCs). Numb-deficient CSCs show unlimited self-renewal and proliferative potential, which is a function of their ability to execute unchecked self-renewing symmetric divisions. These phenotypes that can be reverted by Numb-p53 restoration in a Numb-knockout mouse model, arguing that targeting Numb-p53 dysfunction in Numb-deficient human breast cancer could represent a novel anti-CSC therapy. Using patient-derived xenografts, we have recently demonstrated that expansion of the CSC pool, due to altered self-renewing divisions, is also a distinguishing feature of naturally occurring Numb-deficient human breast cancers. In these cancers, using the inhibitor Nutlin-3 to restore p53, we corrected the defective self-renewal properties of Numb-deficient CSCs and inhibited CSC expansion, thus curbing tumorigenicity and metastasis. Remarkably, a regimen combining Nutlin-3 and chemotherapy-induced persistent tumor growth inhibition, or even regression, and prevented CSC-driven tumor relapse after removal of chemotherapy. We, therefore, provided a pre-clinical proof-of-concept that targeting Numb-p53 dysfunction results in a specific anti-CSC therapy in Numb-deficient human breast cancers. We will discuss the value of the CSC paradigm to address breast cancer heterogeneity and how functional assays based on the biology of CSCs should complement the currently used RECIST criteria for the evaluation of the efficacy of novel anti-cancer therapeutics, in the ultimate perspective of developing effective mechanism-based therapies to eradicate breast cancer.

daniela.tosoni@ieo.it

**Notes:**