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Titolo	A ROLE FOR MYC IN THE SELF RENEWAL OF MAMMARY STEM CELLS AND CANCER STEM CELLS [Tesi di dottorato]
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Sommario	Cancer Stem Cells (CSCs) are a clinically relevant population at the apex of the inner hierarchical organization of many tumors. It was previously demonstrated by our group that loss of the p53 tumor suppressor leads to an increase in the mammary stem cell (MaSC) and breast CSC content, due to a switch of the mode of division from mainly asymmetric to symmetric. However, which of the many pathways instructed by p53 is directly involved in the execution of this biological phenotype remains to be determined. Following a candidate gene approach, we investigated Myc as the putative key downstream effector of p53 in breast SCs and CSCs. The Myc oncogene is very often altered in cancer and has been clinically associated with poor differentiation and aggressiveness in breast cancer. We have found that Myc endogenous expression is de-regulated in our ErbB2 model of breast tumorigenesis, upon attenuation of p53 signaling. We also observed that de-regulated Myc extends the lifespan and proliferative potential of wild type mammospheres. This occurs by two distinct but cooperative mechanisms: the increase in the frequency of symmetric divisions of MaSCs and the reprogramming of progenitor cells. Importantly, in the ErbB2 model, de-regulated Myc levels are critical and sufficient to sustain the unlimited self-renewal of CSCs, independently of p53.

	Of note, the above described phenotype is characterized by the over expression of a mitotic gene signature which is dictated by the identified p53-Myc axis. Taken together these results demonstrate that the loss of a tight control on Myc levels, which derives from the loss of p53 functionality, is responsible for the expansion of the SC and CSC pool by regulating modality of SC division and reprogramming of mammary progenitors. Finally, our data suggest that the p53-Myc axis exerts a putative tumor suppressor function in SCs through the coordinated regulation of a set of mitotic genes.
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