NF1-C2 and its Role in the Mammary Gland

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ABSTRACT

Breast cancer is the most frequently diagnosed cancer among women throughout the world. It arises due to disturbances in the activity or expression of specific factors regulating normal mammary gland growth and differentiation, leading to uncontrolled and abnormal division of cells. In the search for the underlying causes of breast cancer, it is therefore necessary to identify the mechanisms regulating normal proliferation and maturation of the gland.

The work presented in this thesis is aimed at identifying and characterizing transcriptional regulators that are important for adult mouse mammary development. We have identified the transcription factor NF1-C2 as an important player during the developmental cycles of the mammary gland. NF1-C2 upregulates the milk genes carboxyl ester lipase (CEL) and whey acidic protein (WAP) during pregnancy, and is hence important for the functional maturation of the gland. Interestingly, NF1-C2 also actively regulates the tumor suppressor gene p53 during mammogenesis. The role of p53 in the mammary gland is to protect the mammary epithelium from carcinogenesis during pregnancy, and to regulate involution after weaning. We found that the p53 mRNA levels varied during mammary development with high levels during pregnancy, low levels at lactation and high levels during involution. The levels of p53 mRNA were tightly correlated with the levels of NF1-C2 protein during mammogenesis, supporting our conclusion of a role for NF1-C2 in p53 transcriptional regulation. Our results show that the dramatic reduction of NF1-C2 protein levels at the lactation stage is posttranscriptionally regulated. NF1-C2, characterized as a ~50 kDa phosphoprotein, regulates the p53 and milk genes by binding to NF1 binding sites in their promoters. Prevention of this binding resulted in a drastic reduction of the promoter activity in mammary epithelial cells. Furthermore, we present data showing that another NF1 protein isoform, NF1-A1, is present in the mouse mammary gland but not involved in milk gene or p53 regulation which is at least partly due to its lower affinity to the NF1 binding sites of these genes.

We also demonstrate that the pituitary hormone prolactin plays a direct role in maintaining the nuclear levels of NF1-C2 proteins in the mouse mammary epithelium. Prolactin is fundamental for the establishment of the mammary gland. It acts as a mitogen on the mammary epithelium through different pathways, such as the well-characterized Jak-Stat pathway. Our studies suggest that NF1-C2 might represent another transcription factor through which prolactin controls mammary development. Furthermore, our data implies a link between prolactin and p53, mediated by NF1-C2. This suggests that prolactin exerts both proliferative and antiproliferative signaling in the gland, contributing to the finely tuned balance required for proper regulation of mammary gland development.

Keywords: nuclear factor 1-C2, carboxyl ester lipase, p53, mammary gland, prolactin, transcriptional regulation, development.

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