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Adopting mammary development gameplay in breast cancer initiation and progression

The process by which the breast changes during puberty and lactation is incredibly unique. Those changes are essential for the functional mammary gland. These changes are triggered and orchestrated by hormones. Such hormonal changes start during pregnancy and continue while and after the lactation.

The breast is composed of glands and branching ducts surrounded by fibers and fat containing cells that resemble a shape of a tree. During pregnancy breast ducts start to proliferate and form branches and their terminal cells differentiate and form cells that can secrete milk in cellular sacs called alveoli. After the end of lactation, the mammary tissue returns to its nonfunctional state. Overall lot of cellular differentiation and de-differentiation dynamics is involved in this process.

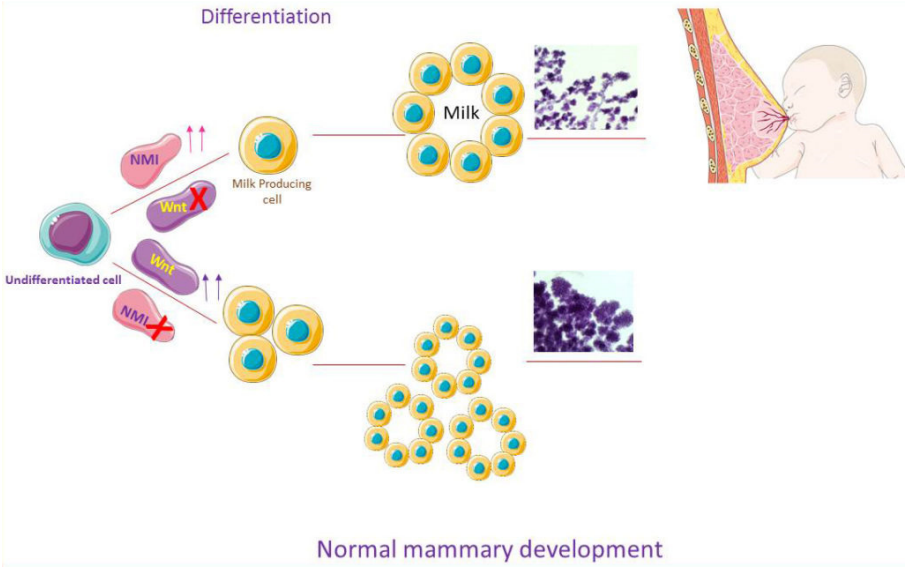

Fig. 1. Schematic illustration of the role of NMI in normal mammary development during pregnancy and lactation. Loss of NMI leads to increase of the number of alveoli and uncontrolled proliferation of the mammary tissues. This figure was created using Servier Medical Art templates (https://smart.servier.com.)

The cell differentiation is the process by which the stem cells (parental cells) undergo changes to be more committed and specialized to a certain cell type (daughter cells). Cancer cells lose differentiation and become immortal, rapidly proliferating and sometimes invasive. Differentiated cancer cell resemble normal cells, which tends to grow and spread slowly and are less aggressive. In fact, it is well documented that cancer adapts developmental processes to aid cancer initiation and progression.

In our study, we found increase in expression of a protein called NMI (N-Myc and STAT Interactor) in mouse mammary tissues during pregnancy and lactation, which gives an impression in its role in mammary tissues development. NMI protein expression was significantly less in breast cancer and its reduction was more evident with more advanced stages of cancer, specifically in metastatic cancer.

To investigate NMI role in mammary development and cancer we deactivated (Knockout) NMI specifically in mouse mammary tissues using a Cre-mediated technology where NMI protein levels decreased to virtually undetectable level in the mammary tissue of knockout mice. We then examined the changes in female mammary gland during different stages of development.

NMI knockout mice showed increase in ductal tree branching and extensions during puberty and an increase in the number of alveoli. The knockout mice successfully lactated their pups. Mammary tissues from knockout mice showed high levels of cellular proliferation markers when compared with mice mammary tissues with NMI. To investigate how loss of NMI contributed to those changes we performed RNA sequencing analysis on mammary tissues at the first day of lactation. Cellular development, growth, and proliferation functions were significantly altered with the loss of NMI. Moreover, an important signaling called Wnt was significantly activated. Wnt signaling is an active part of mammary gland development and uncontrolled promotion of this pathway causes abnormal ductal extension and premature alveolar development. To confirm these finding we stained mouse tissues for activated Wnt and apparently, it is activated in the NMI knockout mice (Fig. 1).

As we mentioned before, cancer steals the developmental mechanism to aid cancer initiation and progression, that's why we studied the effect of deactivating NMI in mouse who are susceptible to form breast cancer (BC) in their lifetime. We found that these mice had BC earlier in their lifetime, and their cancers were rapidly growing and significantly larger. Moreover these mice had more cancer spreading (metastasis) to their lungs. Their tumor cells were more aggressive in nature and showed higher portions of less differentiated-aggressive cells, compared to the tumors with activated NMI. Using data from breast cancer patient's tumors to analyze effects of NMI loss, we found it is indeed through its regulation of Wnt proteins (Fig. 2).

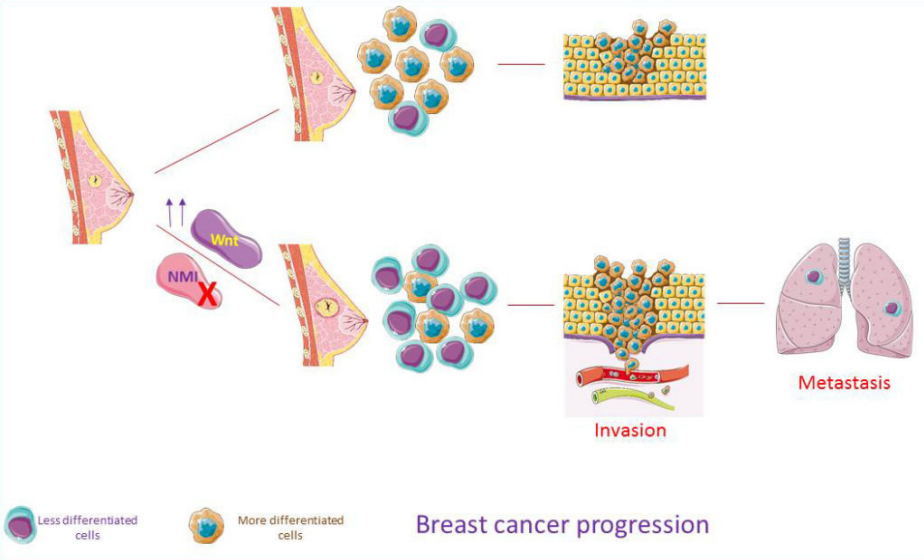

Fig. 2. Schematic illustration for the role of NMI during cancer progression: Upon the loss of NMI BC had higher proportion of less differentiated cells (Blue cells) which tends to form larger tumor and metastasize to the lungs. This figure was created using Servier Medical Art templates (https://smart.serv ier.com.)

Overall, our study shows that understanding the nature of normal mammary development and the disturbance of its fine balance will give insight into BC behavior and characteristics and possibility to identify novel BC treatment.

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Publication

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