LAY ABSTRACT

TITLE: C/EBPβ LIP and c-Jun synergize to regulate expression of the murine progesterone receptor

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The hormone progesterone and its receptor are important in development of the breast and changes in the expression of the progesterone receptor have been associated with breast cancer progression. The progesterone receptor is expressed in two forms, A and B. Increases in receptor A compared to B can be associated with cancer progression, while receptor B is important for a mature breast that can produce milk after pregnancy. The mouse is a useful model system in which to study how the production of the two A and B forms of the progesterone receptor are made from one gene. The mouse is particularly useful because prior to pregnancy and the need for milk production, it makes only progesterone receptor A. But with pregnancy, progesterone receptor A is no longer made, and progesterone receptor B is made instead. This is simpler than in humans, where both receptors are made at the same time. C/EBPβ is a protein that regulates genes required for development of the breast and its ability to produce milk. There is a similar requirement for progesterone receptor B in breast development and the ability to produce milk. This similarity between the roles of the regulatory protein C/EBPβ and progesterone receptor B led us to ask whether C/EBPβ helps regulate progesterone receptor B in a mouse model. We found C/EBPβ can turn on the gene for the progesterone receptor and that a form of C/EBPβ called LIP that is usually inhibitory not only turned on the progesterone receptor gene, but also strongly cooperated with another regulatory protein called c-Jun to drive strong expression of the gene. We found that both C/EBPβ and c-Jun proteins sit on the DNA in the regulatory region of the progesterone receptor gene. When we looked in pregnant mice that turn on expression of the progesterone receptor B gene in preparation for making milk, we saw that both progesterone receptor B and the LIP form of C/EBPβ increase at the same time. Consistent with a role for LIP in controlling progesterone receptor B expression, C/EBPβ and progesterone receptor A expression are not expressed in the same cells within the mouse mammary gland, while C/EBPβ and progesterone receptor B are expressed in

the same cells. Our data suggest a critical role for C/EBPβ, particularly the LIP form of C/EBPβ, in progesterone receptor B expression. In the future, it will be interesting to see if there are changes in the production of C/EBPβ proteins that accompany changes in the production of progesterone receptors A and B in human breast cancer progression.