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C/EBPβ and mammary epithelial cell fate

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Keywords

C/EBPβ, cell fate, mammary gland, progesterone receptor

Introduction

Mice which lack the gene encoding the transcription factor C/EBPβ exhibit a severe inhibition of mammary gland lobuloalveolar development. Deletion of the progesterone receptor (PR) gene in the mouse has demonstrated that the expression of PR is necessary for lobuloalveolar development of the mammary gland in response to oestrogen and progesterone. However, alveolar development can be rescued if PR-/- mammary epithelial cells (MEC) are mixed in close proximity to PR+/+ MEC in cleared mammary fat pads, indicating a juxtacrine mechanism of PR action.

Aims

To analyse PR expression in C/EBPβ-/- mice.

Comments

The data presented in this paper indicate that the disruption of C/EBPβ-governed regulatory mechanisms alters the distribution of steroid-receptor-positive mammary epithelial cells and the proliferative response to steroid hormones. Alteration of the mechanisms that control cell fate in the normal mammary gland may contribute to the formation of breast tumours. Recent evidence that steroid receptors are expressed in proliferating tumour cells, but not in proliferating normal epithelial cells (*Am J Pathol* 1999, **155**:1811-1815), suggests that alterations in cell fate may play a role in tumorigenesis. However, more data are needed to support such a hypothesis.

Methods

The mammary glands of C/EBPβ+/+ and -/- virgin mice of various ages were treated with oestrogen and progesterone and analysed for cell proliferation using bromodeoxyuridine (BrdU); PR expression was detected using immunofluorescence. C/EBPβ and PR mRNA expression was also quantified by northern blot analysis and *in situ* hybridisation.

Results

In the mammary glands of wild-type mice, PR- and BrdU-positive cells were adjacent to each other and rarely colocalized. The number of PR-positive cells, as well as the levels of PR mRNA, were elevated threefold in the mammary glands of C/EBPβ-/- mice. Furthermore, in contrast to wild-type nulliparous mice, C/EBPβ-/- mice exhibited uniform PR distribution throughout all stages of mammary development analysed. The overexpression and disrupted cellular distribution of PR in C/EBPβ-/- mice were coincident with a striking 10-fold decrease in cell proliferation after acute steroid hormone treatment.

Discussion

These data suggest a model in which C/EBPβ governs cellular fate in mammary epithelium through the appropriate temporal and spatial expression of molecular markers, such as PR, that induce the proliferation of alveolar progenitor cells via juxtacrine mechanisms. Disruption of these control mechanisms may result in inhibition of MEC proliferation, as observed in the C/EBPβ-/- mouse model, and hypothetically may contribute to the formation of breast tumours in which an altered distribution of steroid hormone receptors has been reported.

References

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