Hormonal deprivation through ovariectomy sensitizes BPA-induced mammary stem cell hyper-proliferation in high fat diet treated mice

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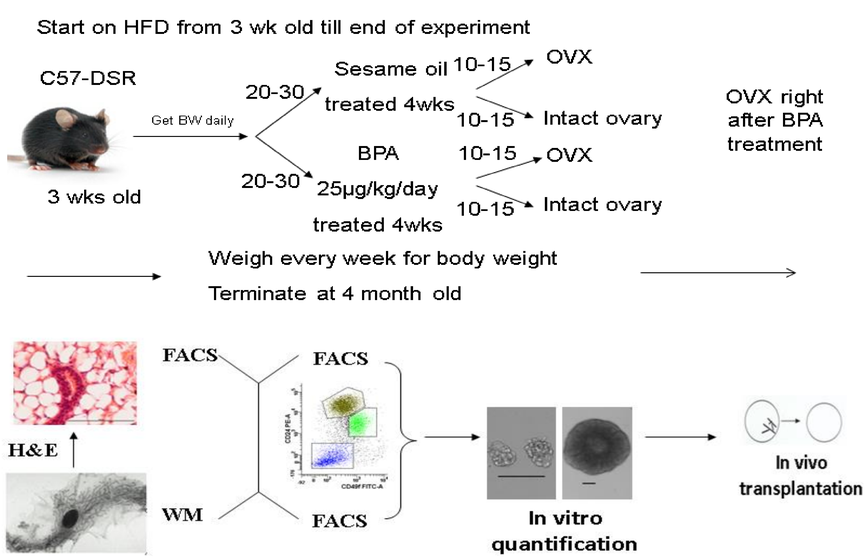
Introduction

The plastic monomer and plasticizer bisphenol A (BPA) is a xenoestrogen that is ubiquitous in the environment and human body. Perinatal exposure to low doses of BPA in rodents caused pre-neoplastic ductal hyperplasia and increased susceptibility to tumorigenesis in the mammary glands. Our recent study revealed that pubertal BPA exposure altered mammary stem cell (MaSC) function leading to early neoplasia in regenerated glands. More recently, weight increase or obesity has been identified as an important risk factor for breast cancer in postmenopausal women. In the present study, we used C57BL/6 mice to evaluate the effect of low dose BPA exposure at puberty and/or ovariectomy on mammary gland development and transformation potential, and whether any adverse effects observed are related to changes of the number and/or function of MaSCs.

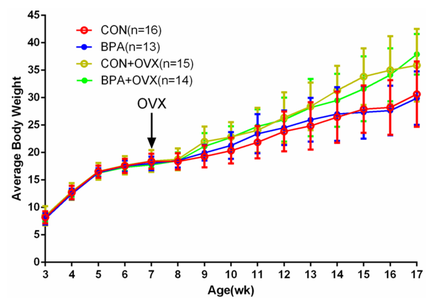
Methods

We exposed 21-day old C57BL/6 mice to BPA by gavage at 25 µg/kg/day during puberty for 4 weeks while all mice were fed with a high fat diet (HFD). Half of mice in each treatment group at 7-week-old were subjected to ovariectomy (OVX) to mimic the postmenopausal scenario. Mammary glands were harvested at 4-month-old for MaSC function analysis using an in vitro mammosphere formation and differentiation assay as well as the in vivo cleared mammary fat pad regeneration assay.

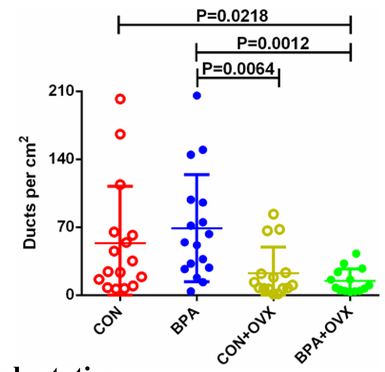


Results

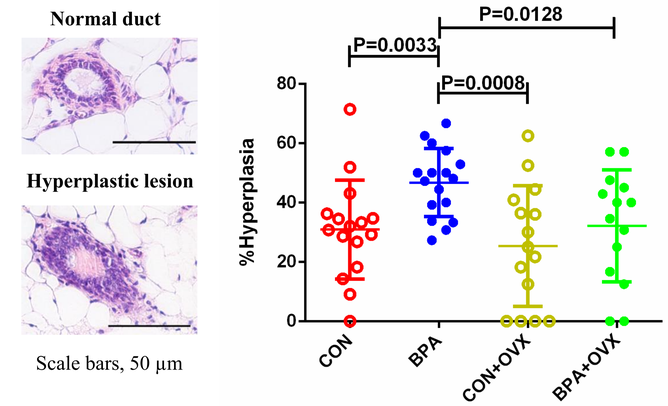
Body weight



Mammary ductal area



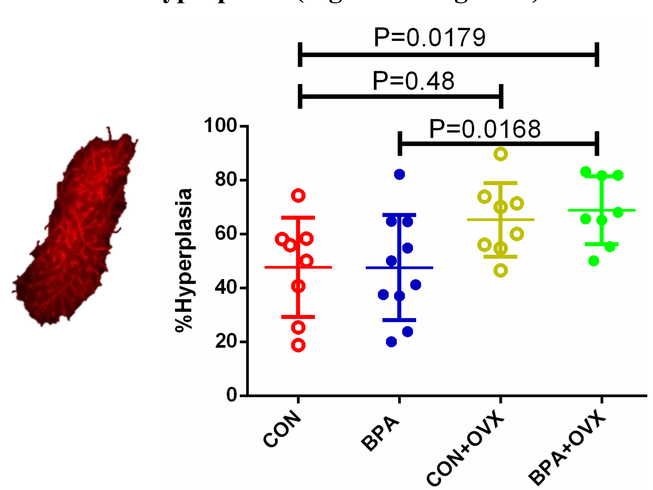
Hyperplasia (primary glands)



In vivo cleared fat pad transplantation

Treatment	Number of Outgrowth	%Fat Pad Filled
CON	9/10	
BPA	10/10	
CON+OVX	9/10	
BPA+OVX	7/10	

Hyperplasia (regenerated glands)



Conclusions

- Body weight: no significant difference between control and BPA, but higher body weight gain was found in all OVX mice.
- MaSC number and frequency: no significant difference among all treatment groups; however, mammary epithelia in BPA, OVX, and OVX+BPA treated mice were biased towards luminal lineage when compared with controls on the HFD without OVX.
- %Hyperplasia: increased in regenerated glands derived from MaSCs isolated from BPA-treated OVX mice when compared regenerated glands from MaSCs isolated from the control and BPA-treated mice.
- Our findings suggest that hormonal deprivation through OVX sensitizes BPA-induced MaSC hyper-proliferation on a HFD background.

Acknowledgements

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