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High fat diet promotes prostatic basal-to-luminal differentiation and accelerates initiation of prostate epithelial hyperplasia originated from basal cells☆

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ABSTRACT

Recent lineage tracing studies showed that the prostate basal and luminal cells in adult mice are two independent lineages under the physiological condition, but basal cells are capable of generating luminal progenies during bacterial infection-induced prostatitis. Because acute bacterial infection in human prostate tissues is relatively rare, the disease relevance of the bacterial infection-induced basal-to-luminal differentiation is uncertain. Herein we employ a high fat diet-induced sterile prostate inflammation model to determine whether basal-to-luminal differentiation can be induced by inflammation irrespective of the underlying etiologies. A K14-CreER model and a fluorescent report line are utilized to specifically label basal cells with the green fluorescent protein. We show that high fat diet promotes immune cell infiltration into the prostate tissues and basal-to-luminal differentiation. Increased cell proliferation accompanies basal-to-luminal differentiation, suggesting a concurrent regulation of basal cell proliferation and differentiation. This study demonstrates that basal-to-luminal differentiation can be induced by different types of prostate inflammation evolved with distinct etiologies. Finally, high fat diet also accelerates initiation and progression of prostatic intraepithelial neoplasia that are originated from basal cells with loss-of-function of the tumor suppressor Pten. Because prostate cancer originated from basal cells tends to be invasive, our study also provides an alternative explanation for the association between obesity and aggressive prostate cancer.

1. Introduction

Understanding how prostate epithelial lineage hierarchy is maintained is important since it helps reveal how prostate-related diseases including benign prostatic hyperplasia (BPH) and prostate cancer are initiated and progressed (Xin, 2013; Kwon & Xin, 2014; Lawson et al., 2005). There are three types of epithelial cells in the prostate (Abate-Shen & Shen, 2000). The secretory luminal cells form a layer surrounding the lumen. The basal cell layer is aligned between the basement membrane and the luminal cells. The neuroendocrine cells are rare and less well characterized. Recent lineage tracing studies including ours showed that basal and luminal cells in adult mice are two independent lineages under the physiological condition (Choi et al., 2012; Liu et al., 2011; Lu et al., 2013; Wang et al., 2013). However, during bacterial infection-induced prostatitis prostate basal cells undergo proliferation and are capable of generating luminal cells (Kwon et al., 2014). This basal-to-luminal differentiation is essential for initiation of prostate cancer with a basal cell origin (Kwon et al., 2014). However, acute bacterial infection in the prostate is relatively rare in human patients (Krieger & Riley, 2002). Therefore, the relevance of the bacterial infection-induced basal-to-luminal differentiation to the human prostate-related diseases is uncertain. In addition, it remains an open question whether basal-to-luminal differentiation is able to be induced by any types of prostate inflammation irrespective of the underlying etiologies.

Obesity has been closely associated with higher risks for BPH progression and aggressive prostate cancer (De Nunzio et al., 2012; Allott et al., 2013). Several studies have demonstrated that intake of high fat diet can induce an inflammatory microenvironment in rodent prostate

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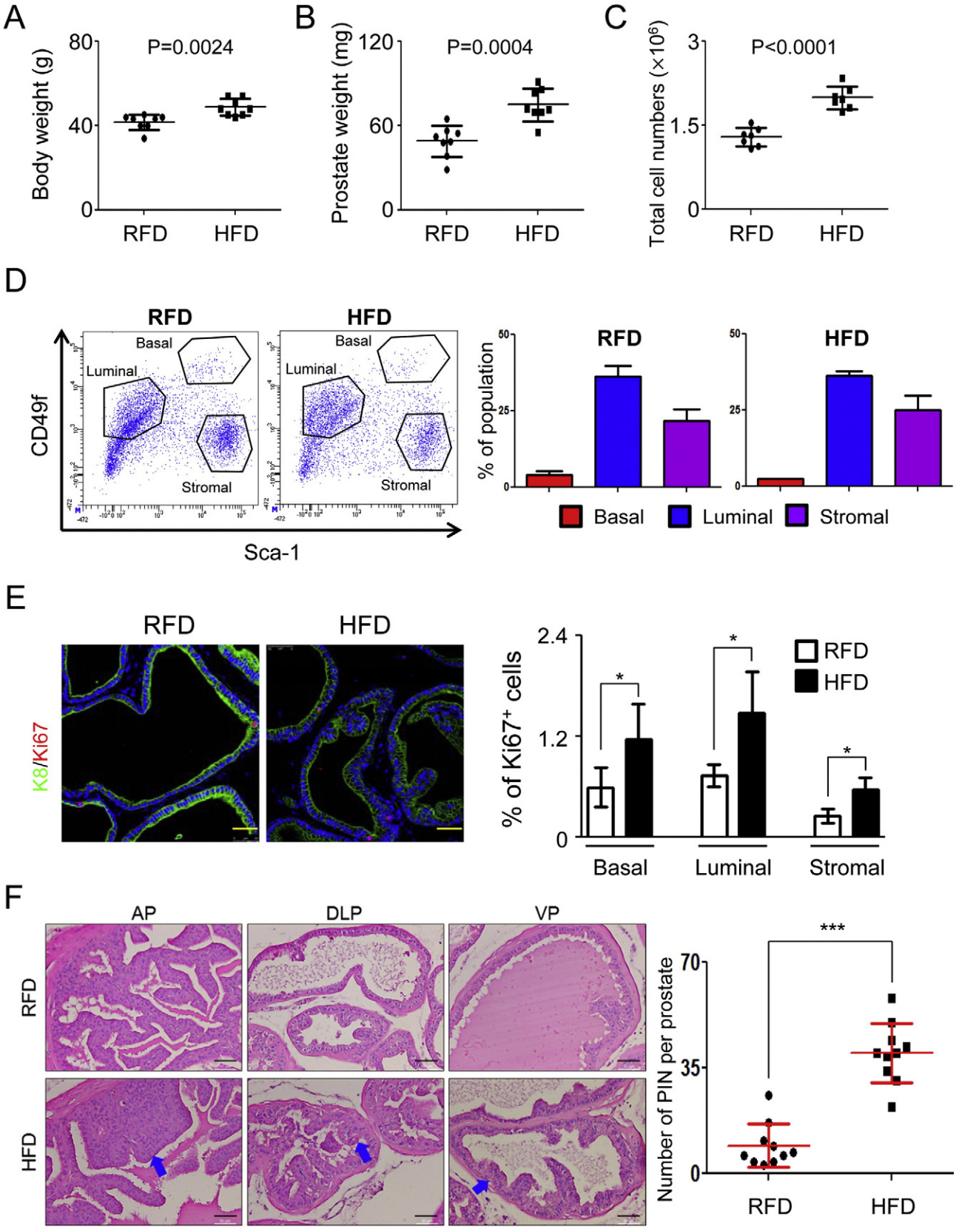

Fig. 1. High fat diet promotes prostate growth. A–C: Dot plots show means ± s.d. of body weight (A), prostate weight (B), and total prostate cell numbers (C) of mice on regular fat diet (RFD) and high fat diet (HFD). N = 8 for each group. D: FACS plots of prostate cell lineages in mice on HFD and RFD diets. Bar graphs show means ± s.d. of cell percentages. E: Coimmunostaining of Ki67 and K8. F: H&E staining of anterior (AP), dorsolateral (DLP), and ventral (VP) prostate lobes of mice on RFD and HFD diets. Bars = 50 μm. Blue arrows point to PIN1 lesions. Dot graph shows means ± s.d. of quantification of PIN per mouse. *:$p < 0.05$, **:$p < 0.01$, ***:$p < 0.001$.