Orlistat exerts anti-obesity and anti-tumorigenic effects in a transgenic mouse model of endometrial cancer

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BACKGROUND

- **Endometrial cancer (EC)**: 4th most common cancer among women in U.S.[1]
  - Increasing in frequency and mortality due to the obesity epidemic.[2]
  - Rise in obesity is directly correlated with rise in EC rates.
- **Fatty Acid Synthase (FAS)** → building block of the cell membrane.
  - Upregulated in many types of cancer cells to promote rapid division and growth.
  - Increased in endometrial cancer, is a reliable indicator of recurrence.[3]
- **Estrogen** binds to the E2 receptor and activates the SREBP-1c gene through both the PI3K/AKT pathway as well as the MEK pathway , promoting fatty acid synthase in cells which then promotes carcinogenesis and increases the metastatic potential of tumor cells[3]
- **Orlistat** → potent FAS inhibitor.
  - Demonstrated to inhibit tumorigenesis in pre-clinical models of EC.[4]

Given the intimate relationship between obesity, increased fatty acid synthase, and EC progression, potent FAS inhibitors such as orlistat may play a role in the treatment and prevention of obesity-driven EC. However, the impact of orlistat in EC pathogenesis remains unexplored.

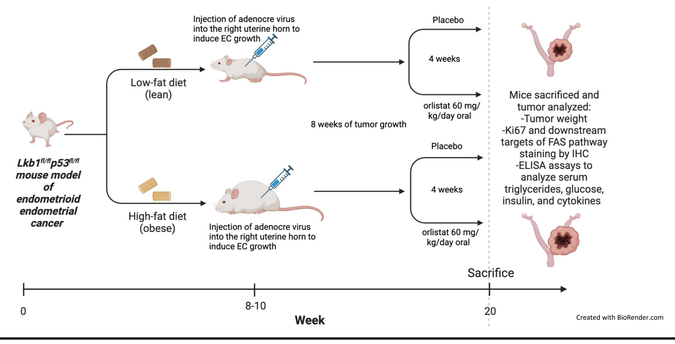
OBJECTIVE: To analyze the anti-proliferative and anti-tumorigenic effects of orlistat in primary cultures of human endometrioid EC cells, as well as in a transgenic mouse model of endometrioid EC.

METHODS

1. Primary culture of human endometrioid EC cells

- Eleven tumor samples collected from patients undergoing hysterectomy for endometrioid EC
- Exposed to orlistat 0.1-500 μM over 72 hours
- Cell proliferation was assessed by MTT assay
- Apoptosis was assessed by cleaved caspase-3 assay, and western immunoblotting was performed to assess effects of orlistat on apoptotic proteins

2. *Lkb1*$^{fl/fl}$*p53*$^{fl/fl}$ mouse model of endometrioid EC



1. Seigel et al. Cancer Statistics. 2021 | 2. Smrz et al. AJOG. 2021 | 3. Lupu & Menendez. Endocrinology. 2006. | 4. Wysham et al. Targeted Oncology. 2016

RESULTS

Figure 1. Orlistat produced anti-proliferative and pro-apoptotic effects in human endometrial cancer cell lines.

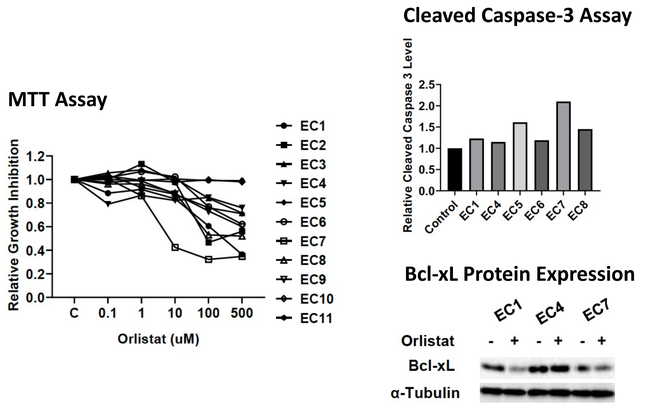


Figure 2. Orlistat decreased body weight in HFD (obese) and LFD (lean)-fed mice. Circulating adipokines were higher at baseline in HFD-fed (obese) mice and were decreased by orlistat treatment.

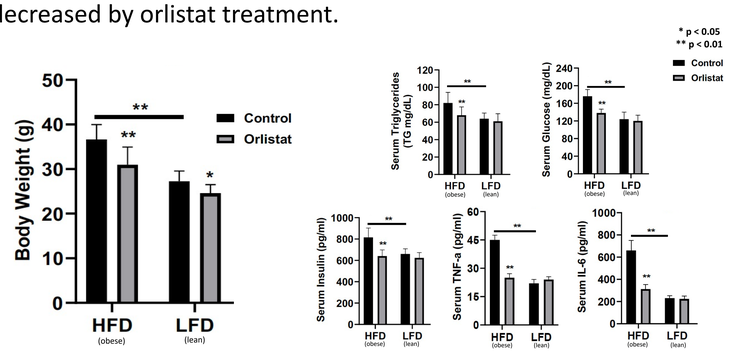


Figure 3. Orlistat induced anti-angiogenesis effects *in vivo*. VEGF and MMP-9 levels were higher at baseline in HFD-fed (obese) mice.

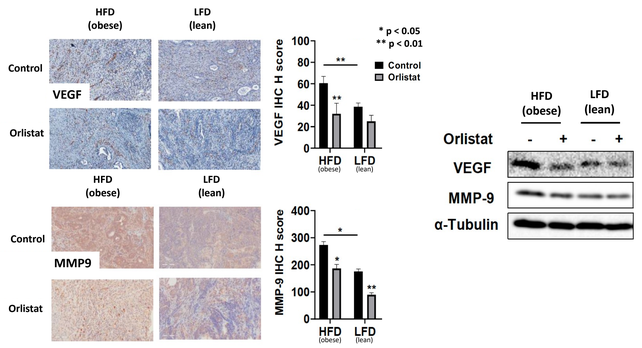
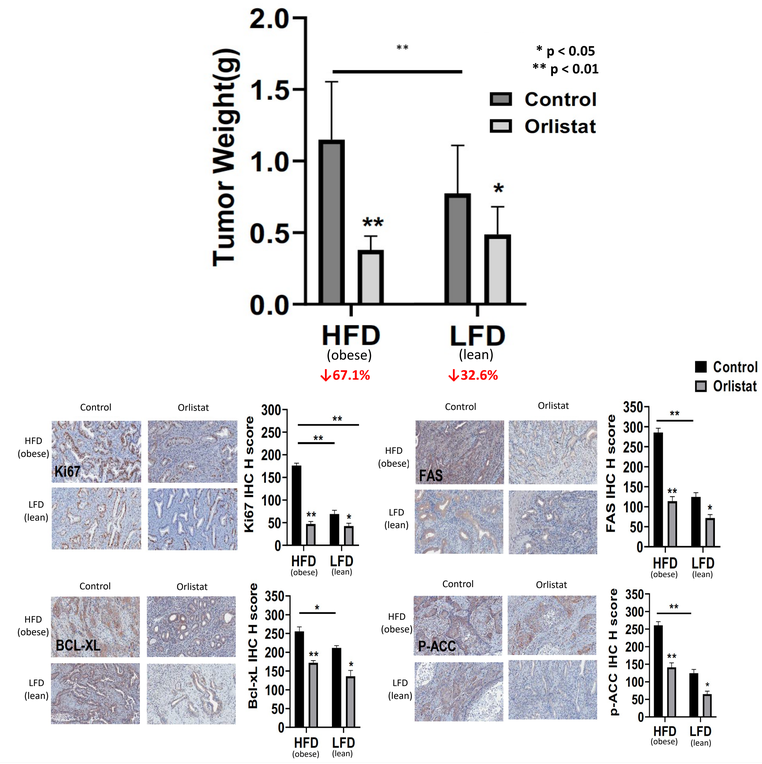


Figure 4. Orlistat induced anti-tumorigenic and anti-proliferative effects *in vivo*



CONCLUSIONS

1. Orlistat inhibited tumor cell proliferation in human endometrioid EC primary culture cells:

- Inhibition of cell proliferation, induction of apoptosis, and downregulation of the anti-apoptotic protein Bcl-xL.

2. Mouse model of endometrioid EC:

- Orlistat decreased body weight, circulating adipokines and markers of metabolic syndrome in a high-fat diet (obese) environment.
- Orlistat decreased tumorigenesis and inhibited EC proliferation in both HFD-fed (obese) and LFD-fed (lean) mice
- In addition, treatment with orlistat demonstrated anti-angiogenic properties in EC tumors in vivo.

Take-away: Further studies are needed to assess if orlistat would be a novel intervention in the prevention and treatment of obesity-driven endometrial cancer.

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