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.
  • Overregulated 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<sup>fl/fl</sup>/p53<sup>ko/ko</sup> mouse model of endometrioid EC

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.