Maresin-1, a specialized-pro-resolving mediator of inflammation, demonstrates anti-tumorigenic activity in obesity-driven endometrial cancer (EC)
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BACKGROUND
- Endometrial cancer: 4th most common cancer among women in U.S.
  - Increasing in frequency and mortality due to the obesity epidemic.
- Obesity induces a chronic inflammatory state which is proposed to drive development of endometrial cancer (EC).
- Central obesity linked to shifts in adipokine profiles and lipolysis, increased inflammatory cytokines and pro-inflammatory eicosanoids.
- Insulin resistance and hyperestrogenism are implicated as proximate causes of EC.
- Decreased levels of specialized pro-resolving lipid mediators (SPMs) of inflammation are linked to insulin resistance and hyperestrogenism.
- One of the main SPMs = maresin-1 possess anti-inflammatory effects in multiple inflammatory mediated diseases.
- SPMs have a protective effect in inflammatory conditions, low levels can fuel carcinogenesis.
- Preclinical studies: Maresin-1 has been shown to inhibit tumorigenesis.

Given the intimate relationship between inflammation and EC progression, it is logical that SPMs may play a role in obesity-driven EC. However, the impact of SPMs, such as maresin-1, in EC pathogenesis remains unexplored.

OBJECTIVE: To evaluate the effect of maresin-1 on tumor growth in the Lkb1fl/flp53+/+ genetically engineered mouse model of endometrioid EC under obese and lean conditions.

METHODS
The effects of maresin-1 were evaluated in the Lkb1fl/flp53+/+ mouse model of endometrioid EC, using the following protocol:

- Effects of maresin-1 were assessed by one-way ANOVA.
- Oxylipin profiling (including SPMs) was performed in both visceral adipose tissue (VAT) and tumor tissue.
- Differences in oxylipins between treatment groups were assessed by one-wall test.

RESULTS
Figure 1. ECs in obese (HFD) vs lean (LFD) mice demonstrated increased lipid biosynthesis and decreased expression of maresin-1 (p<0.05).

Figure 2. Hydroxyeicosatetraenoic acids (HETEs) were lower in the visceral adipose tissue (VAT) in obese (HFD) vs lean (LFD) mice.

Figure 3. Maresin-1 decreased tumor weight and Ki-67 expression in both obese (HFD) and lean (LFD) mice in the Lkb1fl/flp53+/+ mouse model.

CONCLUSIONS
1. Maresin-1 has anti-tumorigenic effects in an endometrioid endometrial cancer mouse model:
   - Significant reduction in endometrial cancer tumor weight and Ki-67 expression.
   - These effects were more pronounced in the setting of obesity.
2. Obesity decreased the production of HETEs in VAT and the anti-inflammatory SPM maresin-1 in EC tumors.

Take-away: Future investigation of maresin-1 as a novel inflammatory-resolving agent for the treatment of EC is warranted.