Maresin-1, a specialized-pro-resolving mediator of inflammation, demonstrates anti-tumorigenic activity in obesity-driven endometrial cancer (EC)

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BACKGROUND

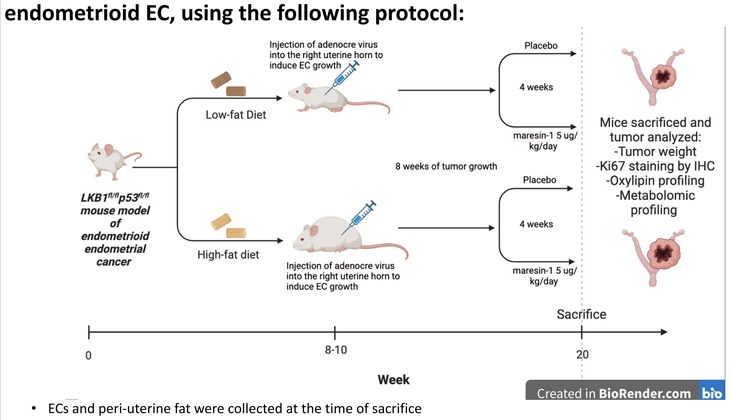
- **Endometrial cancer**: 4th most common cancer among women in U.S.[1]
  - Increasing in frequency and mortality due to the obesity epidemic.[2]
- **Obesity** induces a chronic inflammatory state which is proposed to drive development of endometrial cancer (EC).[3]
- **Central obesity** → linked to shifts in adipokine profiles and lipolysis, increased inflammatory cytokines and pro-inflammatory eicosanoids.[4]
- Insulin resistance and hyperestrogenism are implicated as proximate causes of EC.[4]
- Decreased levels of **specialized pro-resolving lipid mediators (SPMs)** of inflammation are linked to insulin resistance and hyperestrogenism.[5]
- One of the main SPMs = **maresin-1** → potent anti-inflammatory effects in multiple inflammatory mediated diseases.
  - SPMs have a protective effect in inflammatory conditions, low levels can fuel carcinogenesis.[6]
  - Preclinical studies: Maresin-1 has been shown to inhibit tumorigenesis[7]

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 *Lkb1$^{fl/fl}$p53$^{fl/fl}$* genetically engineered mouse model of endometrioid EC under obese and lean conditions.

METHODS

The effects of maresin-1 were evaluated in the *LKB1$^{fl/fl}$p53$^{fl/fl}$* mouse model of endometrioid EC, using the following protocol:



- ECs and peri-uterine fat were collected at the time of sacrifice
- Immunohistochemistry for Ki-67 was performed to assess the effects of maresin-1 on proliferation
- Mass spectroscopy was performed to evaluate metabolomic profiles (Metabolon) from tumor tissue
- 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-way ANOVA or Kruskal-Wallis test

1. Seigel et al. Cancer Statistics. 2021 | 2. Smrz et al. AJOG. 2021 | 3. Onstad et al. Journal of Clinical Oncology. 2016 | 4. Yang et al. Frontiers in Oncology. 2019 | 5. Martinez-Fernandez et al. The Journal of Physiology and Biochemistry. 2021. | 6. Lavy et al. Frontiers in Immunology. 2021 | 7. Mudge et al. AACR Annual Meeting Abstract. 2014.

RESULTS

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

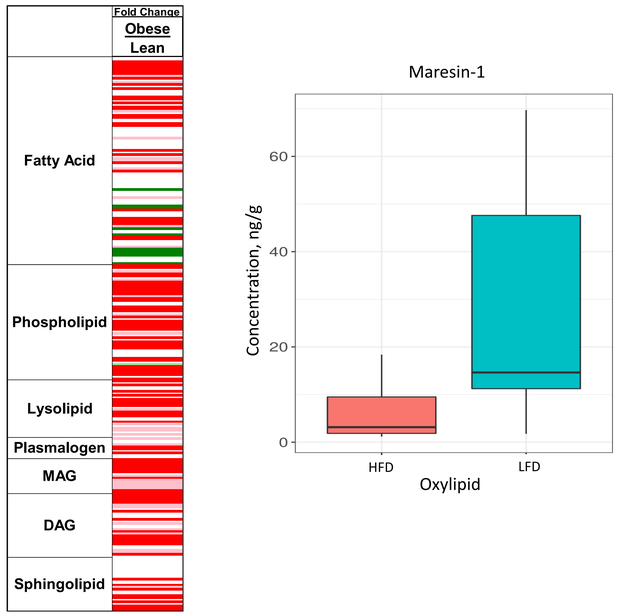


Figure 2. Hydroxyeicosatetraenoic acids (HETEs) were lower in the visceral adipose tissue (VAT) in obese (HFD) *vs* lean (LFD) mice.

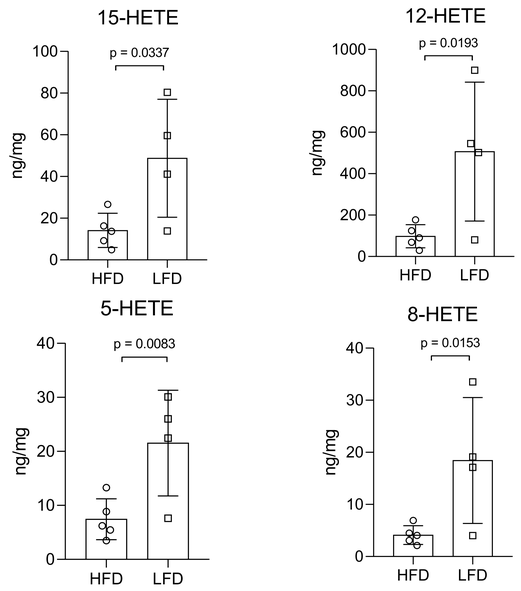
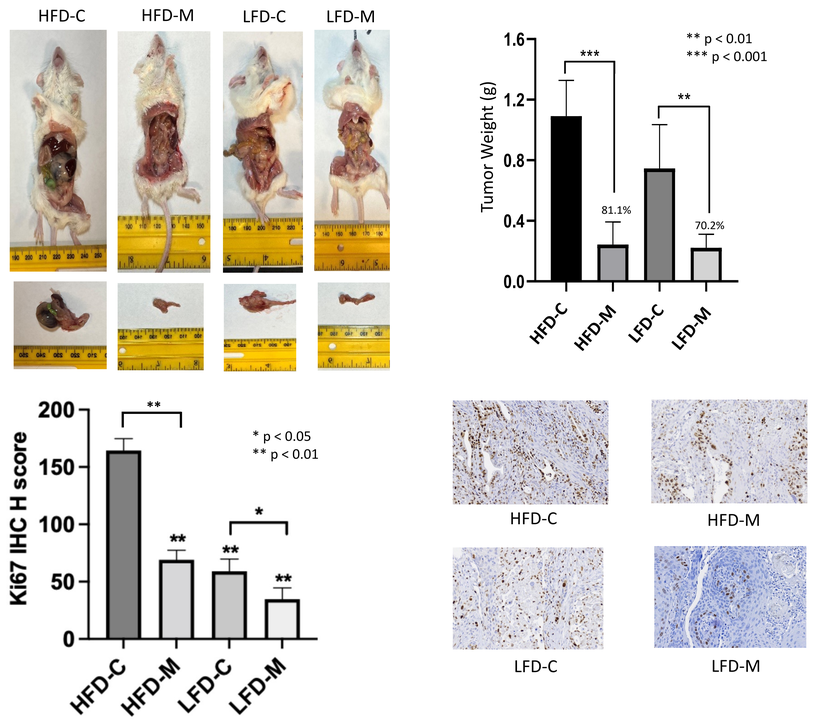


Figure 3. Maresin-1 decreased tumor weight and Ki-67 expression in both obese (HFD) and lean (LFD) mice in the *LKB1$^{fl/fl}$p53$^{fl/fl}$ mouse model.*



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 HETE's 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.

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