Sulindac, a COX1/COX2 Inhibitor, Exhibits Anti-tumorigenic Effects in Obesity-driven Models of Endometrioid 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.\(^2\)
- Obesity induces a chronic inflammatory state which is proposed to drive development of endometrial cancer (EC).\(^3\)
- Adipocytes ⇒ complex endocrine organ\(^4\)
  - Main source of aromatase in post-menopause ⇒ unopposed estrogen
  - Modulates activity of IGF1 and IGF1R ⇒ stimulate endometrial proliferation through MAPK and AKT signaling pathways
  - Secretion of pro-inflammatory adipokines such as leptin, IL-6, TNF-α ⇒ leads to insulin resistance and increased levels of IGF1\(^5\), promoting hyperactivity of the MAPK and PI3K/AKT/mTOR pathways.
- Sulindac ⇒ potent anti-inflammatory effects through inhibition of the COX1 and COX2 pathways.
  - Sulindac has demonstrated promising effects in pre-clinical models of obesity driven GI cancer

Given the intimate relationship between obesity, inflammation, and EC progression, anti-inflammatory drugs may have potential in the prevention and treatment of obesity-driven EC. However, the impact of sulindac in EC pathogenesis remains unexplored.

OBJECTIVE: To analyze the effects of sulindac on tumorigenesis and tumor development in endometrioid EC cell lines and in a transgenic mouse model of endometrioid EC.

METHODS

1. Human endometrioid endometrial cancer cell lines: KLE, HEC-1
   - Exposed to sulindac at varying concentrations and studied by:
     - Cell proliferation (MTT assay, colony count assay)
     - Apoptosis (Cleaved Caspase-3, -8, -9 assays)
     - Cellular stress (Reactive oxygen species (ROS), JC-1, and TMRE assays)
     - Migration determined by wound healing assay
     - Western immunoblotting to assess sulindac’s effects on downstream targets related to cellular stress, apoptosis, cell cycle control and DNA damage

2. Lkb1\(^{-/-}\)p53\(^{+/+}\) mouse model of endometrioid endometrial cancer

RESULTS

Figure 1. Sulindac inhibited cell proliferation in dose-dependent fashion by MTT assay (left) and colony count assay (right).

Figure 2. Induction of apoptosis in a dose-dependent fashion by sulindac.

Figure 3. Sulindac increased cellular stress in a dose-dependent fashion.

Figure 4. Sulindac inhibited cell invasion in vitro.

Figure 5. Sulindac decreased cell cycle proteins (A) and downregulated COX-2 (B).

Figure 6. Sulindac inhibited tumor growth and decreased Ki-67 and COX-2 expression in the Lkb1\(^{-/-}\)p53\(^{+/+}\) mouse model.

CONCLUSIONS

Sulindac has anti-tumorigenic and anti-proliferative effects in endometrioid EC:
- Inhibition of cell proliferation, induction of apoptosis, increased cellular stress, inhibition of cell invasion and decreased cell cycle proteins.
- Significant reduction in EC tumor weight, Ki-67 expression and COX-2 expression. These effects were more pronounced in the setting of obesity.

Take-away: Further studies are needed to assess if sulindac would be a novel intervention in the treatment of endometrial cancer.