Anti-inflammatory drug resistance in breast and colon cancer stem cells: Preclinical leads

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Rationale:

Cancer incidence and molecular subtypes: Breast and colon cancer together represent major organ site cancers in women. The American Cancer Society projects 268,600 and 49,730 new cases, and 41,760 and 23,380 cancer related deaths for breast and colon cancer, respectively in 2020 (1). Based on their genetic, molecular and hormonal characteristics, these organ site cancers are classified as Luminal A, Luminal B, HER-2-enriched and triple negative for breast, and genetically predisposed and sporadic for colon (2, 3). Conceptual and mechanistic links evidenced by clinical and preclinical data suggests that similar to breast cancer, colon cancer may also be hormonally related. Thus, loss of 17β-estradiol (E2) and ER signaling in post-menopausal women may contribute to breast and colon carcinogenesis (4, 5).

Therapeutic options: Human epidermal growth receptor-2 (HER-2) expressing breast cancers in the presence of hormone receptors (Luminal B subtype) or in the absence of hormone receptors (HER-2-enriched subtype) respond to distinct endocrine and HER-2 signaling pathway targeted therapeutic options (6, 7). Genetically predisposed and sporadic colon cancer respond to epidermal growth factor receptor (EGFR) signaling pathway, to non-steroid anti-inflammatory drugs (NSAID) and to selective cyclo-oxygenease-2 inhibitors (COXIB) based therapeutic options (8, 9). Status of estrogen receptor-β (ER-β) has been correlated with genetically predisposed and sporadic colon cancer in women (10). In ER-α and ER-β deficient mice, loss of function of adenomatous polyposis coli (Apc) tumor suppressor gene accelerates colon carcinogenesis (11). Pharmacological therapeutic agents such as aromatase inhibitors (AI), NSAIDs and COXIBs may be associated with acquired tumor resistance and resultant emergence of drug resistant cancer stem cells.

Testable alternatives: Natural phytochemicals such as cruciferous glucosinolate, soy isoflavone, rosemary terpenoids, and curcumin have documented growth inhibitory efficacy via mechanistically distinct pathways in preclinical cellular models in vitro (12, 13), and in animal models in vivo (14-16). Drug resistant stem cell models for breast and colon cancer exhibit susceptibility to natural products (17-19). Non-toxic natural products are unlikely to exhibit tumor resistance, and therefore, may offer testable alternatives against therapy resistant cancer stem cells.

- Objectives: This presentation will discuss
- Drug resistant stem cell models,
- Effects of select natural products and
- Future directions to enhance clinical translatability

Experimental Models: Recent experimental approaches utilize clinically relevant models for breast and colon cancer where gain of function of human epidermal growth factor receptor-2 (HER-2) oncogene in breast or loss of function of Apc tumor suppressor gene in colon represent cancer subtype specific primary genetic defects that drive the carcinogenic process. These cellular models include tumorigenic HER-2 positive human breast epithelial 184-B5/HER cells for the HER-2-enriched subtype (20) and Apc negative colonic epithelial 850MIN COL cells generated from genetically predisposed Apc [+/-] C57BL/J6-Min/+ female mice, a model for genetically predisposed colon subtype (21). Similar to NSAIDs and COXIBs, naturally-occurring growth inhibitory terpenoids and retinoic acid receptor selective vitamin A derivatives (13, 22) inhibit inducible COX-2 activity in the present HER-2 positive 184/B5/HER model (23, 24).

Experimental Evidence: HER-2 positive breast model and Apc negative colon model exhibit hyper-proliferation as evidenced by accelerated cell cycle progression and downregulated cellular apoptosis. Treatment with the NSAID sulindac (SUL) selects and enriches drug resistant SUL-R stem cells that are characterized by the emergence of tumor spheroids, upregulation of cell surface stem cell markers CD44 and CD133, and upregulation of molecular stem cell markers c-Myc, NANOG and OCT-4. The stem cell markers are monitored by a quantitative immuno-fluorescence assay that measures cellular

fluorescence of antibody positive cells. Natural products such as vitamin A derivative all trans retinoic acid (ATRA), Rosemary terpenoid carnosol (CSOL) and bio-active agent from Turmeric curcumin (CUR) downregulate stem cell specific cellular and molecular marker expression and inhibit growth of cancer stem cells. Collectively, this evidence validates an experimental approach to evaluate and prioritize efficacious natural products as agents capable of targeting cancer stem cell population by identifying susceptible mechanistic pathways and potential molecular targets.

Conclusion: Present preclinical approaches using models for breast and colon cancer stem cells identify clinically translatable leads for natural products as testable alternatives for therapy resistant cancer.

Future prospects: Present stem cell targeted experimental approaches (17, 25, 26) provide a scientifically robust basis for patient derived tumor organoid (PDTO) models from clinical therapy resistant tumor samples (27-29). This direction should enhance clinical translatability.

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