Inflammation (Latin, *inflammatio*, "I ignite, set alight") is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process.

Cancers have wound-like environments such as hypoxia and acidic extracellular pH – ‘tumors are wounds that do not heal’ (Dvorak, NEJM, 1986)

Prostanoid biosynthetic cascade. Arachidonic acid (AA) is released from membrane phospholipids by the hydrolyzing action of phospholipases. AA is metabolized by lipoxygenases (LOXs) to form leukotrienes, by P450 isozymes to form epoxyeicosatrienoic acids, and by COX enzymes to form prostanoids. The COX product PGE2 is further metabolized by specific syntheses to yield prostaglandins and thromboxanes, which bind prostanoid receptors to evoke a wide array of biological effects.

The characteristic response of living vascularized tissue to injury is inflammation, which induces the formation of eicosanoids. Three well-known classes of phospholipases, phospholipase A2 (PLA2), phospholipase C (PLC) and PLD, participate in the formation of free arachidonate from membrane phospholipids in response to mechanical, chemical and physical stimuli.

AA is converted to various eicosanoids by the action of lipoxygenases (LOX) and cyclooxygenases (COX). These eicosanoids impact on cell motility, invasion, vascular characteristics and metastatic dissemination.

Most solid tumors, including breast cancers, exhibit inflammatory properties characterized by increased levels of prostaglandins and other proinflammatory molecules that are secreted by tumor cells, stromal cells, and specialized immune cells during inflammation.

COX-1 (constitutive form) and COX-2 (inducible form) are cytoplasmic enzymes that convert PLA2-mobilized AA into the lipid signal transduction molecules prostaglandins and thromboxanes. COX-2 function has been the target of pharmaceutical intervention in a multitude of widespread degenerating conditions, including autoimmune diseases, gastric inflammation, and several different cancers, such as gastric, lung, breast, and colon cancer. Its expression is induced by proinflammatory cytokines, such as interleukins (IL)-1β and tumor necrosis factor (TNF)-α, and its promoter contains a cyclic AMP response element, a nuclear factor-κB binding site, and two nuclear factor for IL-6 target sequences.
**Studying the role of COX-2 in cancer**

Persistent pro-inflammatory stimuli

- Membrane phospholipids
- iPLA2
- Arachidonic acid
- COX-2
- TXA2
- PGI2
- TXS
- PGE2
- PTGIS
- PGES
- cPLA2
- COX-2
- PGH2
- PGE2

NSAIDs: aspirin, naproxen, indomethacin

COX-2 selective inhibitors: celecoxib, rofecoxib, valdecoxib

- Immunity
- Inflammation
- Development
- Labor
- Neurodegeneration
- Arthritis
- Cancer
- Asthma

COX-1 is not affected by the inflammatory process - gastroprotective

COX-2 is not detectable in normal tissue, but is detectable after induction by inflammatory stimuli.

COX-2 selective inhibitor celecoxib in clinical trials:
- 309 past, present or planned
- 174 in cancer
- 23 recruiting

Celecoxib is given as chemoprevention in patients with Familial Adenomatous Polyposis

Selective COX-2 inhibitors are thought to increase the risk of adverse cardiovascular reactions

COX-2 is expressed in 40% of primary breast tumors

Clinical inflammation (edema) is not necessarily required for COX-2 expression in the microenvironment.

**COX-2 and cancer: a quick perspective**

<table>
<thead>
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<th>Search string</th>
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<td>Prognosis cancer</td>
<td>2010</td>
<td>VEGF cancer</td>
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Source: www.clinicaltrials.gov

**Silencing of COX-2 in MDA-MB-231 cells**

<table>
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<th>Incubation time (h)</th>
<th>COX-2</th>
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<tr>
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**Silencing of COX-2 delays tumor onset in SCID mice**

<table>
<thead>
<tr>
<th>Incubation time (h)</th>
<th>MDA-MB-231</th>
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<th>Clone 2</th>
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**Accumulation of fluorocoxibs in the inflamed paw**

Carageenan was injected into the paw at time zero. After 24 h, the fluorocoxib was administered by intraperitoneal injection.

**Xenograft data on uptake of fluorocoxib A**

Fluorocoxib A was administered by retro-orbital injection and the animals monitored for fluorescence 3.5 h later using a Xenogen camera. The head-and-neck cancer, 1483, expresses COX-2 whereas the colon cancer, HCT116, does not express COX-2.

**Clone 2: Clone stably transfected with a plasmid coding for a COX-2 shRNA**

**Pooled: Pool of four clones stably transfected with the COX-2 shRNA plasmid**

**Tumor volume (mm³)**

<table>
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<tr>
<th>Time (days)</th>
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**Incubation time (h)**

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**Stasinopoulos et al., Mol. Cancer Res. 2007**

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**Targeting COX**

- Greek physician Hippocrates (c. 460 BC – c. 370) prescribed an extract from willow bark and leaves. In the 17th century, the active ingredient of willow bark salicin was identified in Europe. The Kolbe company in Germany started mass producing salicylic acid in 1860.

- Acetylsalicylic acid 1 (Aspirin) was introduced by Bayer in 1899.

- John Vane (in the seventies) discovered the mechanism of action of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).


**Evolution of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Cyclooxygenase (COX) Inhibition and Beyond**

- P. N. Praveen Rao1 and Edward E. Knaus2.

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Targeting COX – non specific effects

<table>
<thead>
<tr>
<th>Class</th>
<th>Properties</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>NSAIDs that inhibit both COX-1 and COX-2, completely with little selectivity</td>
<td>Aspirin, ibuprofen, diclofenac, indomethacin, naproxen, piroxicam, celecoxib, etodolac, ketorolac, tenoxicam, meloxicam</td>
</tr>
<tr>
<td>Group 2</td>
<td>NSAIDs that inhibit COX-2 with a 5-50 fold selectivity</td>
<td>Naproxen, ketoprofen, ibuprofen, celecoxib</td>
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<tr>
<td>Group 3</td>
<td>NSAIDs that inhibit COX-2 with a &gt; 50 fold selectivity</td>
<td>Ibuprofen, indomethacin</td>
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<tr>
<td>Group 4</td>
<td>NSAIDs that are weak inhibitors of both isoforms</td>
<td>Aminopyrine, sodium salicylate, salicylate, stilbazolium</td>
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</tbody>
</table>

GI side effects associated with traditional NSAIDs are due to the inhibition of gastroprotective PGs synthesized via the COX-1 pathway.

Acknowledgements

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