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INFLAMMATION: PATHOGENESIS, PREVALENCE AND MANAGEMENT

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ABSTRACT

Inflammation is a pervasive form of defense that is broadly defined as a nonspecific response to tissue malfunction and is employed by both innate and adaptive immune systems to combat pathogenic intruders. Inflammation is combination of various immunological, physiological, and behavioral processes that are organized by soluble immune signaling molecules called cytokines.

Keywords: Inflammation, Pathogenesis, Prevalence and Management

INTRODUCTION

Inflammation and its types

Inflammation is a pervasive form of defense that is broadly defined as a nonspecific response to tissue malfunction and is employed by both innate and adaptive immune systems to combat pathogenic intruders **[1]**. Inflammation, in its broadest sense, is a host response to tissue injury which involve defense reaction resulting elimination of injurious agent necrosed cells or tissue. The four ancient, cardinal, signs of inflammation described by Roman writer Celsus are redness, heat, swelling, and pain while loss of function was described by Virchow **[2, 3]**.

Causative agents [3]

- Infective agents (bacteria, viruses, fungi, parasites etc)
- Immunological agents (cell mediated and antigen-antibody reactions),
- Physical agents (heat, cold, radiation, mechanical trauma etc)
- Chemical reagents (Organic and inorganic poison),

- Inert material (foreign particle like dust, pollen etc).

Classification of inflammation

Depending upon the defense capacity of host and duration response inflammation may classify as acute and chronic inflammation **[3]**.

❖ **Acute Inflammation**

Acute inflammation is the immediate and early response to injury lasting less than two week which involve leukocytes and plasma proteins as a mediator of host defense. It is characterized by following **(Figure 1)**.

- Alteration in vascular caliber that lead to increase in blood flow.
- Elimination of plasma protein and leukocytes from circulation and accumulation at site of inflammation.
- Activation of polymorphonuclear neutrophils for elimination of offending agent.

❖ **Chronic Inflammation**

Chronic inflammation can be considered to be inflammation of prolonged duration (weeks to months to years in which active inflammation, tissue destruction, and attempt for healing of injurious cell proceed simultaneously. It occurs if causative agents of acute inflammation persist for long time, autoimmunity and exposure of potentially toxic substance either exogenous or endogenous. It is characterized by following **(Figure 2)**.

- Infiltration with mononuclear cells which including macrophages, lymphocytes, and plasma cells
- Tissue destruction induced by offending agent or, inflammatory cells
- Attempt of healing at connective tissue replacement of damage tissue accomplished by angiogenesis and fibrosis.

PATHOGENESIS

Inflammation is combination of various immunological, physiological, and behavioral processes that are organized by soluble immune signaling molecules called cytokines. The pathogenesis of inflammation depend upon following steps **[1] (Figure 3)**.

- Recognition of infection or damage
- Activation of common signaling pathways
- Release of pro inflammatory cytokines
- Recruitment of effecter cells
- Polarization of Inflammation
- Resolution of Inflammation

Initiators of inflammation such as pathogens, environmental factor, physical factors etc when comes in contact with cells or tissue they produce injury to them which recognized with the help of innate immune system and pathogen-associated molecular patterns (PAMPs), which are specifically directed toward general structures of molecules expressed by pathogens that are essential for pathogen survival.

Many damage signals are recognized by germ-line encoded receptors, such as trans membrane Toll-like receptors (TLRs) and intracellular nucleotide binding domain (NOD-like receptors) and nucleotide binding leucine-rich-repeat- containing receptors (NLRs) which activate common signaling pathways responsible for release of NF-κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) from inhibitor protein, IκB in all type of cells. Activated NF-κ B binds with target genes in nucleus and produce transcription.

Transcription and translation of genes lead to release of proinflammatory cytokines, such as interleukin-1-beta (IL- 1β), IL-6, tumor necrosis factor-alpha (TNF-α), and others. The release of these chemokines facilitates the recruitment of effector cells, such as monocytes and neutrophils, to the site of disturbance in conjugation with various co stimulatory molecules. These cells produce highly reactive oxygen and nitrogen species and various proteinases which destructive to both pathogens and hosts and essentially induce liquefaction of surrounding tissue to protect from microbial metastasis and initiate conventional cardinal signs of local inflammation: heat, swelling, redness, pain, and loss of function.

These cells then migrates to prime naive T cells (Th0; never exposed to antigen) in lymphoid tissue and bound to MHC class II receptors. After that naive T cells produce different types of effector and regulatory cells: Th1 and Th17 cells (pro-inflammatory), Th2 cells (anti-inflammatory) and regulatory T-cells (Tregs).Th1 cells and Th17 cells produces cytokines (IFN-γ, IL-2, NF-α) (IL-17, IL-6, NF-α) respectively which are important for initiation of delayed type hypersensitivity responses and macrophage activation. Th2 cells produce a different characteristic set of anti-inflammatory cytokines, such as IL-4, IL-5, IL-10, and IL-13 that promote alternative activation of macrophages, and responsible for conversion of B-cell antibody to IgE and eosinophil maturation , while down regulating it produce Th1 cytokines hence responsible for inflammation. Treg cells secrets IL-10 and TGF-β which regulate

homeostasis of the immune system by moderating Th1 and Th2 responses.

The last phase of inflammation is its resolution which start after few hours of inflammation lipoxin produced by macrophages which block further neutrophil recruitment and increases uptake of monocytes which responsible for wound healing.

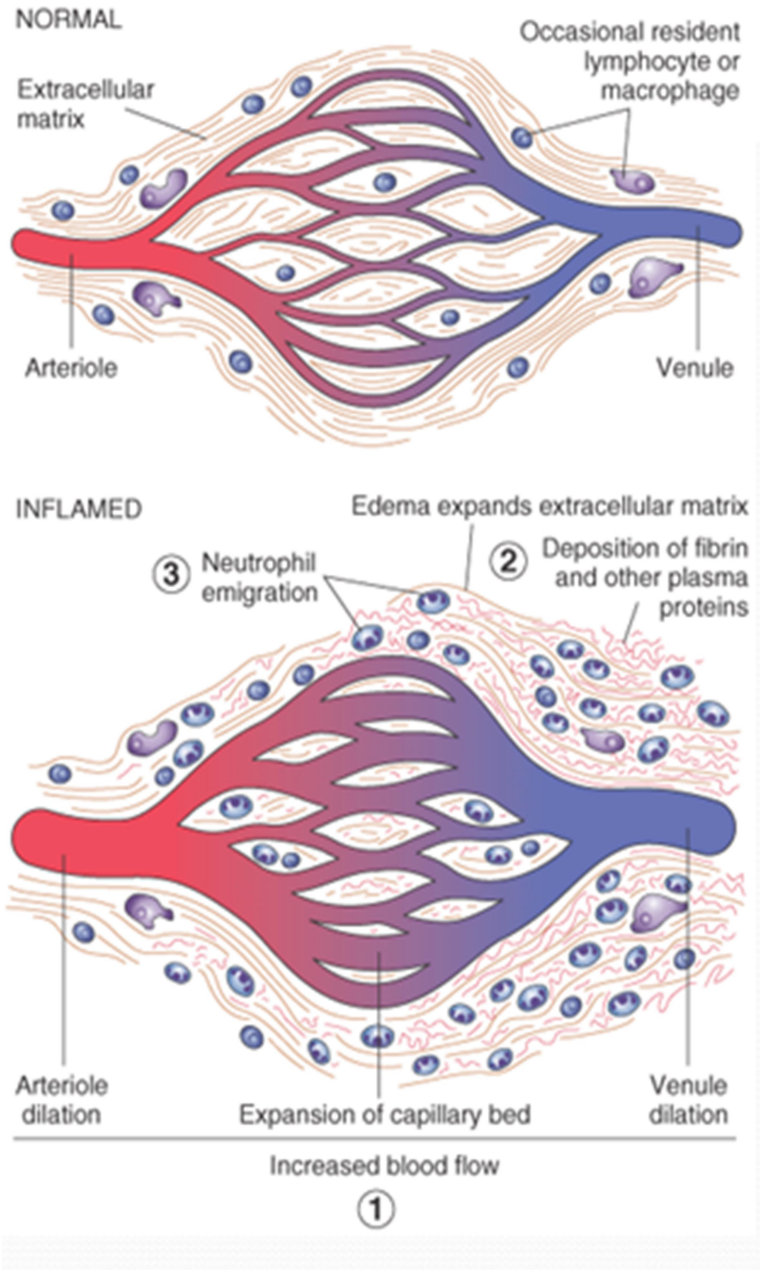

Figure 1: Mechanism of acute inflammation

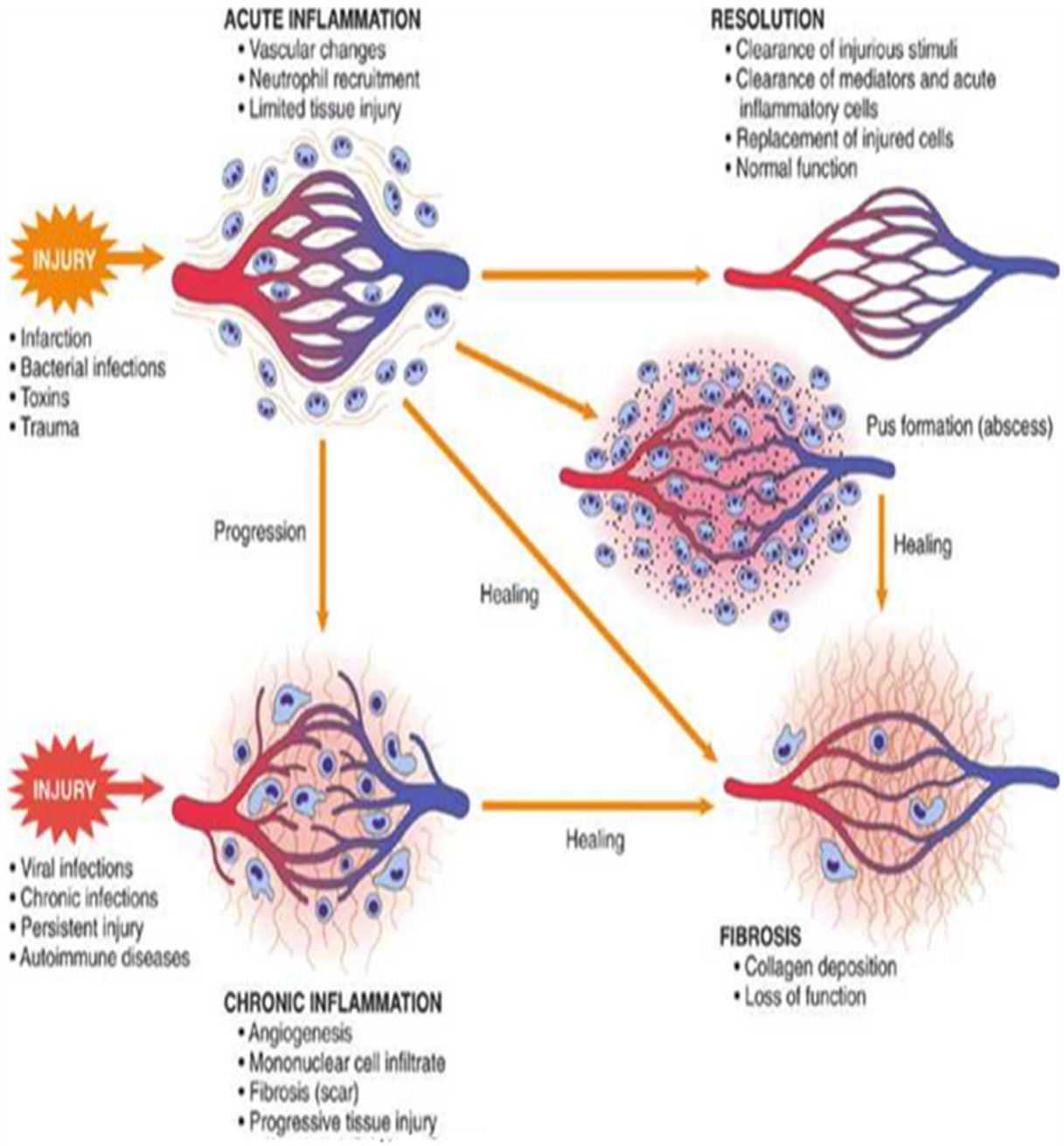

Figure 2: Mechanism of chronic inflammation

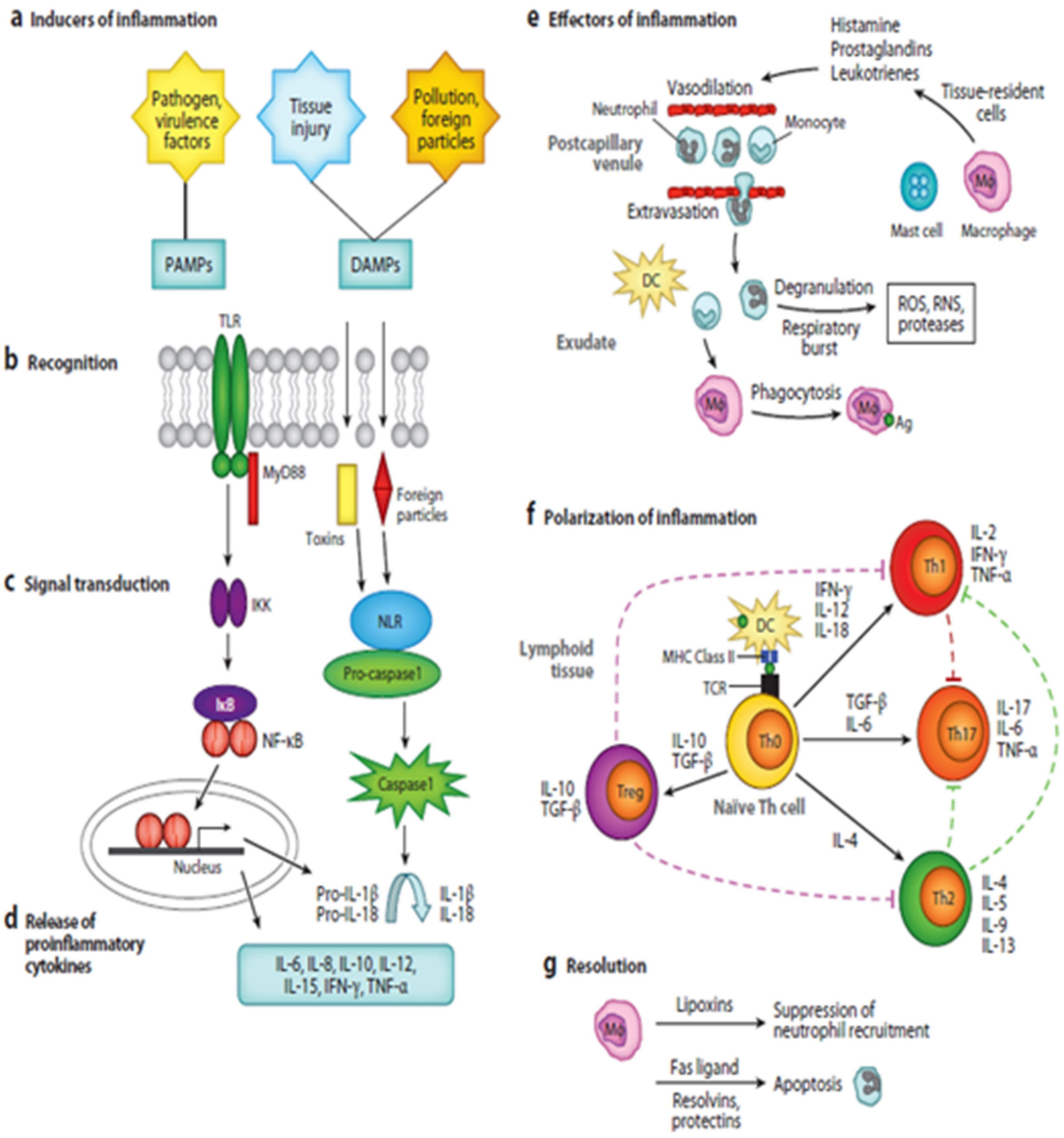

Figure 3: Pathogenesis of inflammation

DIAGNOSIS

Redness, heat, swelling, and pain are very common parameter for diagnosis of inflammation while catabolically generated edema is the only specific macroscopic sign for diagnosis However, the presence of systematic inflammation detected by presence of various inflammatory mediators such as C-reactive protein (CRP), tumor necrosis factor-α (TNF- α), interleukin 1(IL-1), lipoprotein-associated phospholipase A2 (Lp-PLA2) and Eicosanoids with the help of sophisticated analyzing techniques **[5, 6]**.

TREATMENT

Management of inflammation may involve steroidal anti inflammatory drugs

such as corticosteroids, Non-steroidal anti-inflammatory drugs, Immune Selective Anti-Inflammatory Derivatives (ImSAIDs) such as FEG and SGP-T, phytochemicals and Thermotherapy **[7, 8]**.

NSAIDs are most common and effective therapy for treatment of inflammation which may categorized as per following **[9]**.

- Non selective COX inhibitor
  - ✓ Salicylates: Aspirin
  - ✓ Propionic acid derivatives: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
  - ✓ Fennamate: Mefennamic acid
  - ✓ Enolic acid derivatives: Piroxicam, Tenoxiam
  - ✓ Acetic acid derivatives: Ketorolac, Indomethacine, Nabumeton.
  - ✓ Pyrazole derivatives: Phenylbutazone, Oxyphenbutazone
- Preferntial COX-2 inhibitors

  Nimesulide, Diclofenac, Aceclfenac, eloxicam,Etodolac.
- Selective COX-2 Inhibitor

  Celecoxib, Etoroxib, Parecoxib.

PREVALENCE

With the advancement of molecular pathogenesis it cleared that Pro-inflammatory mediators (cytokines) have significant role in pathogenesis of various diseases like Acquired Immunodeficiency Syndrome (AIDS), Asthma, Cancer, Cardiovascular disorders such as Atherosclerosis, Congestive heart failure, Gastrointestinal disorders such as Peptic ulcer, Crohn's disease, Neurological diseases such as Alzheimer's disease, Down's syndrome, Multiple sclerosis, Diabetes Psychiatric disorders such as Depression, Schizophrenia, Sleep disorders, Stress, Rheumatoid, Arthritis, Sepsis **[10]**.

However as per the survey of American cancer society cardiovascular diseases, Cancer, Respiratory infections, Digestive diseases, and Diabetes mellitus are the leading causes of death worldwide **[11]**. Hence it can estimate that each and every person all over the world may suffer from inflammation.

PLANTS HAVING ANTI-INFLAMMATORY ACTIVITY

Most of plants possess anti-inflammatory properties plays significant role in many inflammatory disorders while purified natural compounds from plants can serve as starting material for the synthesis of new generation anti-inflammatory drugs with low toxicity and higher therapeutic value. Some anti-inflammatory plants with their active phytochemicals are mentioned in **Table 1 [12]**.

Table 1: List of plants having anti-inflammatory activity

S. No	Botanical Name	Common Name	Chemical Constituent
1	*Acacia catechu* Leguminosae	Katha	Tannins catechin, quercetin, catechuic acid.
2	*Amaranthus spinosus* Amaranthaceae	Prickly amaranth	α-spinasterols octacosanoate and saponin.
3	*Asystasia dalzelliana* Acanthaceae	Lavana-valli	Alkaloids, saponins, cardiac glycosides, flavanoids, anthraqui
4	*Butea monosperma* Fabaceae	Palash	Flavonoids, chalcones, tannins.
5	*Calotropis giganteas* Asclepiadaeceae	Crown flower	Calotropnaphthalene, terpenes.
6	*Cassia sophera* Caesalpiniaceae	Kasunda	flavonoids, glycosides
7	*Cissampelos pareira* Menispermaceae	Akanadi	Alkaloids, flavon curine, volatile oil, quercitol.
8	*Cissus quadrangularis* Vitaceae	Hadjod	flavonoids, coumarins, steroids
9	*Cissus rependa* Vitaceae	Pani bel	Alkaloids, glycosides, saponins, tannins.
10	*Dorstonia brasiliensis* Moraceae	Carapia	Monoterpenoid susbstituted furocoumarin, phytosterol.
11	*Elephantopus scaber* Asteraceae	Elephant foot	Glycosides, stigmasterol, deoxyelephantopin
12	*Hibiscus tiliaceus* Malvaceae	Beach Hibiscus	Vanillic acid, syringic acid, β-sitosterol, Quercitin etc.
13	*Holarrhena antidysenterica* Apoynaceae	Indrajao	Alkaloid, Tannins & Flavanoids
14	*Kaempferia galangal* Zingiberaceae	Aromatic ginger	ethyl-p-methoxycinnamate, methylcinnamate, Carvone etc
15	*Leucas cephalotes* Labiatae	Dron pushpi	Alkaloides, terpenes, stigmasterol ,sterols.
16	*Mangifera indica* Anarcardiaceae	Mango	Flavonoids, polyphenolics, triterpenes, tannins
17	*Marsypianthes chanaedrys* Lamiaceae	Konmonmi mawon	Essential oil, germacrene D, betacaryophyllene
18	*Mitragyna parvifolia* Rubiaceae	Kaddam kamgi	pyroligneous acid, methyl acetate, ketones and aldehydes
19	*Oxalis corniculata* Oxalidaceae	Creeping oxalis	alkaloids, steroid, triterpenoids, tannins, flavonoids
20	*Phyllanthus niruri* Phyllanthaceae	Gulf-leaf flower	Flavonoids, sterols, alkaloids, phyllanthin, hypophyllanthin.
21	*Rubia cordifolia* Rubiaceae	Indian Madder	Purpurin, xanthin, glycosides, manjisthin, resins
22	*Solanum trilobatum* Solanaceae	Alarka	Tannins, saponins, flavonoids, cardiac glycosides.
23	*Sterculia foetida* Sterculiaceae	Jangli badam	Fat, cycloprenoid fatty acids.
24	*Tectona grandis* Vervenaceae	sagwan	quinones, steroids, glycosides, flavonoids, alkaloids, saponin

METHODS FOR EVALUATION OF ANTI-INFLAMMATORY ACTIVITY

Various numbers of methods are available for evaluation of anti-inflammatory activity which may divide into in-vitro, in-vivo evaluation for measuring acute inflammation, subacute inflammation and chronic repair processes. The some methods were mentioned bellow **[13]**.

- **In vivo methods for anti-inflammatory activity**
  - 3H-Bradykinin receptor binding
  - Substance P and the tachykinin family
    - ✓ 3H-Substance P receptor binding
    - ✓ Neurokinin receptor binding
    - ✓ Characterization of neurokinin agonists and antagonists by biological assays
  - Assay of polymorphonuclear leukocyte chemotaxis
  - Polymorphonuclear leukocytes aggregation induced by FMLP
  - Constitutive and inducible cellular arachidonic acid metabolism
    - ✓ Formation of leukotriene B4 in human white blood cells
    - ✓ Formation of lipoxygenase products from 14C-arachidonic acid in human polymorphonuclear neutrophils (PMN)
    - ✓ Formation of eicosanoids from 14C-arachidonic acid in human platelets Stimulation of inducible prostaglandin pathway in human PMNL
    - ✓ COX-1 and COX-2 inhibition
  - Induced release of cytokines (Interleukin-1alpha, IL-1beta, IL-6, IL-8 and TNF-alpha) from human white blood cells *in vitro*
  - Flow cytometric analysis of intracellular cytokines
  - TNF-alpha antagonism
  - Binding to interferon receptors
  - Screening for interleukin-1 antagonists
  - Inhibition of interleukin-1β converting enzyme (ICE)
- **In vivo methods for anti-inflammatory activity**
  - Methods for testing acute and subacute inflammation
    - ✓ Ultraviolet erythema in guinea pigs
    - ✓ Vascular permeability
    - ✓ Inhibition of leukocyte adhesion to rat mesenteric venules
    - ✓ Oxazolone-induced ear edema in mice
    - ✓ Croton-oil ear edema in rats and mice
    - ✓ Paw edema

- ✓ Pleurisy test
- ✓ Granuloma pouch technique
- ✓ Urate-induced synovitis

➢ Methods for testing the proliferative phase (granuloma formation)

- ✓ Cotton wool granuloma
- ✓ Sponge implantation technique
- ✓ Glass rod granuloma

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