Table 3-4 Principal Mediators of Inflammation

Mediator	Source	Action
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion, and activation
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	Local: endothelial activation (expression of adhesion molecules). Systemic: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (membrane attack complex), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain

to a stimulus. **The major cell types that produce mediators of acute inflammation are the sentinels that detect invaders and damage in tissues, that is, macrophages, dendritic cells, and mast cells,** but platelets, neutrophils, endothelial cells, and most epithelia can also be induced to elaborate some of the mediators. *Plasma-derived mediators* (e.g., complement proteins) are produced mainly in the liver and are present in the circulation as inactive precursors that must be activated, usually by a series of proteolytic cleavages, to acquire their biologic properties.

- **Active mediators are produced only in response to various stimuli.** These stimuli include microbial products and substances released from necrotic cells. Some of the stimuli trigger well-defined receptors and signaling pathways, described earlier, but we still do not know how other stimuli induce the secretion of mediators (e.g., from mast cells in response to cell injury or mechanical irritation). The usual requirement for microbes or dead tissues as the initiating stimulus ensures that inflammation is normally triggered only when and where it is needed.
- **Most of the mediators are short-lived.** They quickly decay, or are inactivated by enzymes, or they are otherwise scavenged or inhibited. There is thus a system of checks and balances that regulates mediator actions. These built-in control mechanisms are discussed with each class of mediator.
- **One mediator can stimulate the release of other mediators.** For instance, products of complement activation stimulate the release of histamine, and the cytokine TNF acts on endothelial cells to stimulate the production of another cytokine, IL-1, and many chemokines. The secondary mediators may have the same actions as the initial mediators but may also have different and even opposing activities. Such cascades provide mechanisms for amplifying—or, in certain instances, counteracting—the initial action of a mediator.

We next discuss the more important mediators of acute inflammation, focusing on their mechanisms of action and roles in acute inflammation.

Vasoactive Amines: Histamine and Serotonin

The two major vasoactive amines, so named because they have important actions on blood vessels, are *histamine* and *serotonin*. They are stored as preformed molecules in cells and are therefore among the first mediators to be released during inflammation. The richest sources of histamine are the mast cells that are normally present in the connective tissue adjacent to blood vessels. It is also found in blood basophils and platelets. Histamine is stored in mast cell granules and is released by mast cell degranulation in response to a variety of stimuli, including (1) physical injury, such as trauma, cold, or heat, by unknown mechanisms; (2) binding of antibodies to mast cells, which underlies immediate hypersensitivity (allergic) reactions (Chapter 6); and (3) products of complement called *anaphylatoxins* (C3a and C5a), described later. Antibodies and complement products bind to specific receptors on mast cells and trigger signaling pathways that induce rapid degranulation. In addition, leukocytes are thought to secrete some histamine-releasing proteins but these have not been characterized. Neuropeptides (e.g., substance P) and cytokines (IL-1, IL-8) may also trigger release of histamine.

Histamine causes dilation of arterioles and increases the permeability of venules. Histamine is considered to be the principal mediator of the immediate transient phase of increased vascular permeability, producing interendothelial gaps in venules, as discussed earlier. Its vasoactive effects are mediated mainly via binding to receptors, called H_1 receptors, on microvascular endothelial cells. The antihistamine drugs that are commonly used to treat some inflammatory reactions, such as allergies, are H_1 receptor antagonists that bind to and block the receptor. Histamine also causes contraction of some smooth muscles.

Serotonin (5-hydroxytryptamine) is a preformed vasoactive mediator present in platelets and certain neuroendocrine cells, such as in the gastrointestinal tract, and in mast cells in rodents but not humans. Its primary function is as a neurotransmitter in the gastrointestinal tract. It is also a vasoconstrictor, but the importance of this action in inflammation is unclear.

Arachidonic Acid Metabolites

The lipid mediators *prostaglandins* and *leukotrienes* are produced from arachidonic acid (AA) present in membrane phospholipids, and stimulate vascular and cellular reactions in acute inflammation. AA is a 20-carbon polyunsaturated fatty acid (5,8,11,14-eicosatetraenoic acid) that is derived from dietary sources or by conversion from the