CELLULAR AND MOLECULAR IMMUNOLOGY

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ELEVENTH EDITION

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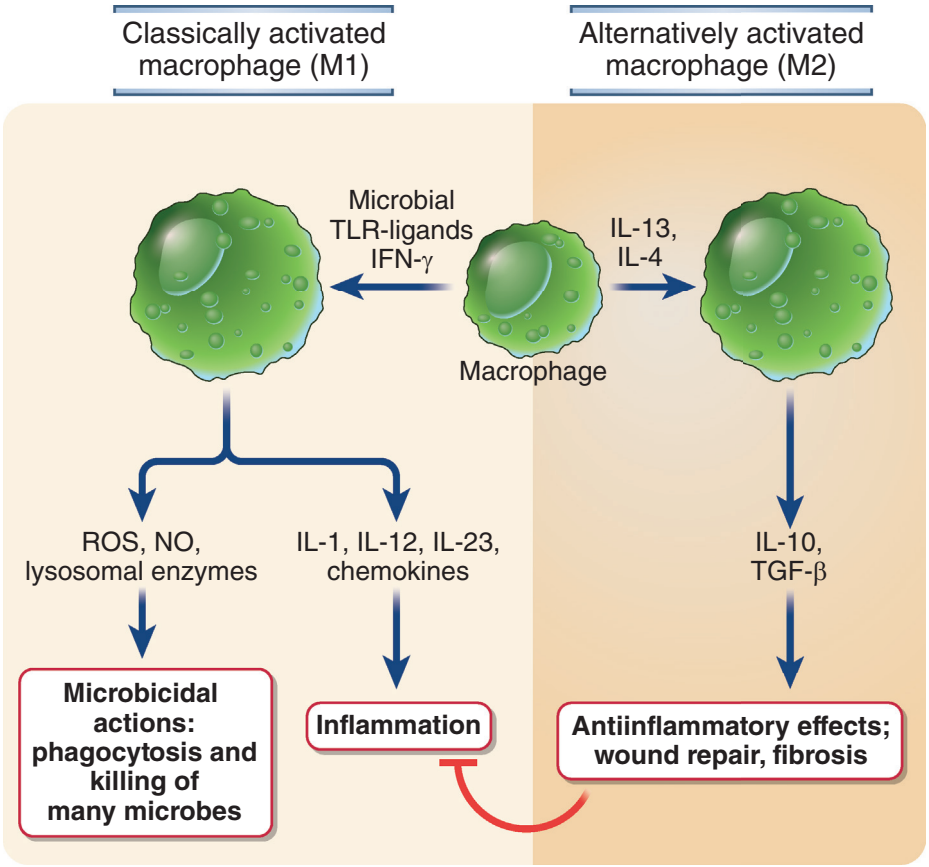

Fig. 10.10 Classical and alternative macrophage activation. Different stimuli activate tissue macrophages to develop into functionally distinct populations. Classically activated macrophages are induced by microbial products and cytokines, particularly interferon-γ (IFN-γ), and are microbicidal and promote inflammation. Alternatively activated macrophages are induced by interleukin-4 (IL-4) and IL-13 produced by Th2 cells and other leukocytes and function to control inflammation and to promote tissue repair and fibrosis. Some evidence suggests that M2 macrophages comprise subpopulations, some of which are mainly anti-inflammatory and others are responsible for tissue repair. *NO*, Nitric oxide; *ROS*, reactive oxygen species; *TGF-β*, transforming growth factor–β; *TLR*, toll-like receptor.

that TGF-β, which is produced by many cell types and is an anti-inflammatory cytokine (see Chapter 15), promotes the development of proinflammatory Th17 cells when other mediators of inflammation, such as IL-6 or IL-1, are present. Th17 differentiation is inhibited by IFN-γ and IL-4; therefore, strong Th1 and Th2 responses tend to suppress Th17 development.

The development of Th17 cells is dependent on the transcription factors RORγt and STAT3 (see Fig. 10.11). TGF-β and the inflammatory cytokines, mainly IL-6 and IL-1, work cooperatively to induce the production of RORγt, a transcription factor that is a member of the retinoic acid receptor family. RORγt is a T cell–restricted protein encoded by the *RORC* gene, so sometimes the protein may be called RORc. Inflammatory cytokines, notably IL-6, activate the transcription factor STAT3, which functions with RORγt to drive the Th17 response.

Th17 cells are abundant in mucosal tissues, particularly of the gastrointestinal tract, suggesting that the tissue environment influences the differentiation and maintenance of this subset, perhaps by providing high local concentrations of TGF-β and inflammatory cytokines. This observation also suggests that Th17 cells may be especially important in combating intestinal infections and in the development of pathologic intestinal inflammation. The development of Th17 cells in the gastrointestinal tract is dependent on the gut microbiome; in mice, commensal bacteria related to *Clostridium* species are potent inducers of Th17 cells.

Functions of Th17 Cells

Th17 cells combat microbes by recruiting leukocytes, mainly neutrophils, to sites of infection (Fig. 10.12). Phagocytosis by neutrophils is a major defense mechanism against many common bacteria and fungi that can survive outside cells but are killed in the phagolysosomes of neutrophils. Th17 cells play an important role in defense against these infections by bringing neutrophils to the microbes. Most of the functions of Th17 cells in host defense are mediated by IL-17, but other cytokines produced by this subset may also contribute.

Interleukin-17

IL-17 is an unusual cytokine because neither it nor its receptor is homologous to any other known cytokine-receptor pair. The IL-17 family includes six structurally related proteins, of which

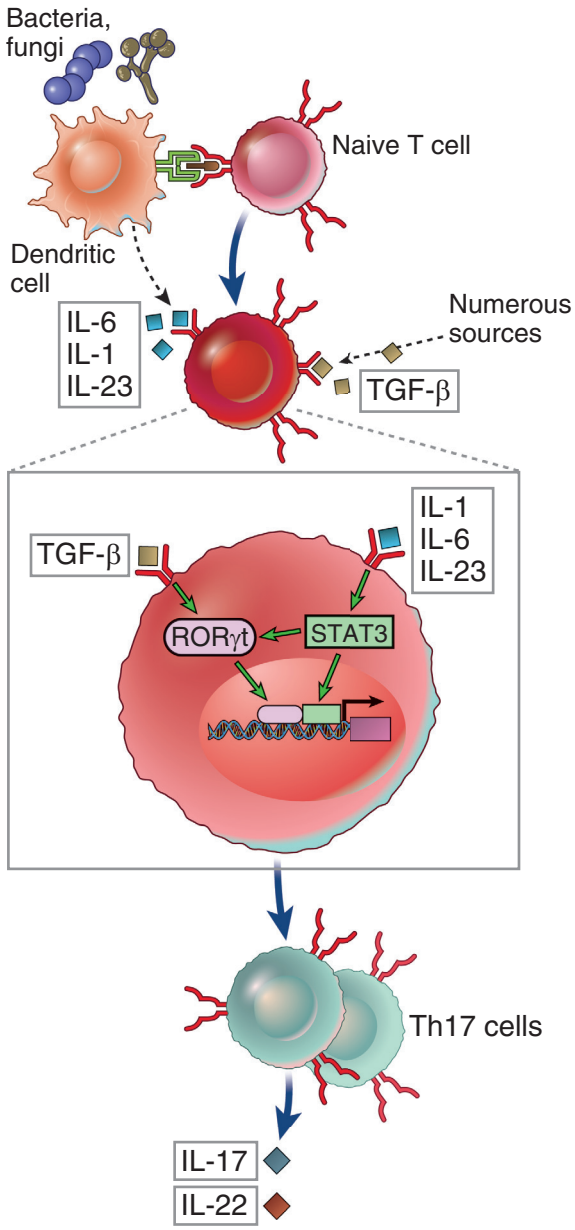

Fig. 10.11 Differentiation of Th17 cells. Interleukin-6 (IL-6) and IL-1 produced by antigen-presenting cells (APCs) and transforming growth factor–β (TGF-β) produced by various cells activate the transcription factors RORγt and STAT3, which stimulate the differentiation of naive CD4+ T cells to the Th17 subset. IL-23, which is also produced by APCs, especially in response to fungi, promotes proliferation of the differentiating Th17 cells. TGF-β may promote Th17 responses indirectly by suppressing Th1 and Th2 cells, both of which inhibit Th17 differentiation (not shown). IL-21 produced by the Th17 cells amplifies this response.

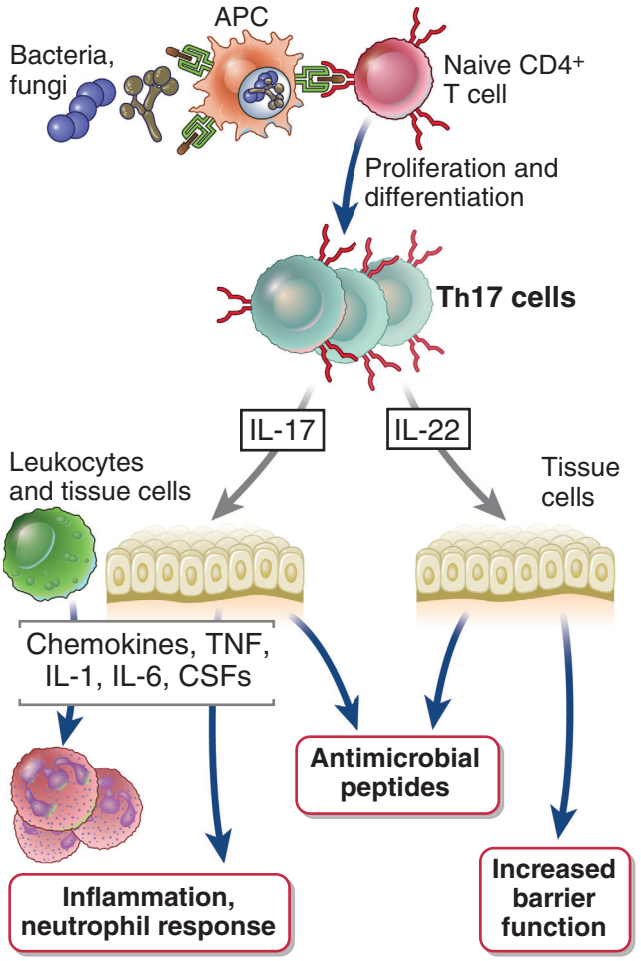

Fig. 10.12 Functions of Th17 cells. Cytokines produced by Th17 cells stimulate local production of chemokines that recruit neutrophils and other leukocytes, increase production of antimicrobial peptides (defensins), and promote epithelial barrier functions. *APC*, Antigen-presenting cell; *CSF*, colony-stimulating factor; *IL*, interleukin; *TNF*, tumor necrosis factor.

IL-17A and IL-17F are the most similar, and the immunologic functions of this cytokine family are mediated primarily by IL-17A. IL-17A is produced by Th17 cells as well as ILC3s and some γδ and CD8+ T cells. IL-17 receptors are multimeric and expressed on a wide range of cells (see Chapter 7). They activate NF-κB and other transcription factors.

IL-17 is an important link between T cell–mediated adaptive immunity and the acute inflammatory response, which we discussed in Chapter 4 as one of the major reactions of innate immunity. When Th17 cells are activated, these reactions are greater in magnitude and more prolonged than what is seen in innate immunity when T cells are not involved.

IL-17 has several important functions in host defense.

- ***IL-17 induces neutrophil-rich inflammation***. It stimulates the production of chemokines, such as IL-8, and other cytokines, such as TNF, that recruit neutrophils and, to a lesser extent, monocytes to the site of T-cell activation. IL-17 also enhances neutrophil generation by increasing the production of granulocyte colony-stimulating factor (G-CSF) and the expression of its receptors. Recruited neutrophils ingest and destroy bacteria and fungi.
- ***IL-17 stimulates the production of antimicrobial substances***, including defensins, from numerous cell types (see Chapter 4).

Other Th17 Cytokines

IL-22 is a member of the type II cytokine family. It is produced by activated T cells, particularly Th17 cells, and by some NK cells and ILCs. The IL-22 receptor is a heterodimer in which

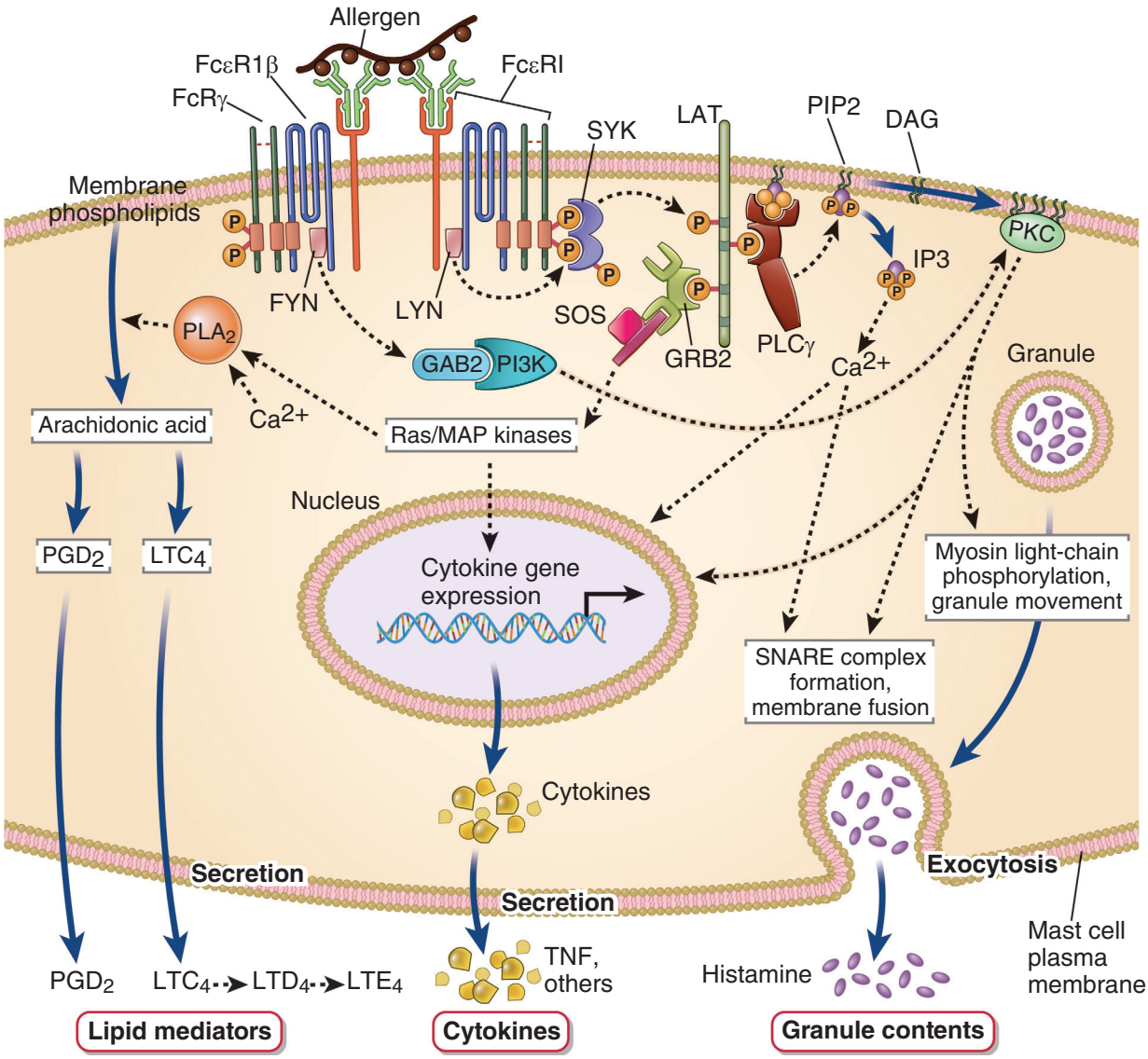

Fig. 20.5 Biochemical events of mast cell activation. Cross-linking of bound IgE by antigen promotes LYN phosphorylation of other signaling molecules, which leads to activation of protein tyrosine kinase SYK, which in turn causes activation of a mitogen-activated protein (*MAP*) kinase cascade and phospholipase Cγ (*PLCγ*). PLCγ catalyzes the release of inositol trisphosphate (*IP3*) and diacylglycerol (*DAG*) from membrane phosphatidylinositol 4,5-bisphosphate (*PIP2*). IP3 causes the release of intracellular calcium from the endoplasmic reticulum. Calcium and DAG activate protein kinase C (*PKC*). FYN phosphorylation of GAB2 leads to PI3K activation, which contributes to PKC activation. Calcium, MAP kinases, and PKC promote cytokine gene transcription, leading to secretion of cytokines. PKC and calcium also enhance granule exocytosis, releasing histamine and other preformed mediators. Calcium and MAP kinases combine to activate the enzyme cytosolic phospholipase A_2 (*PLA_2*), which initiates the synthesis of lipid mediators, including prostaglandin D_2 (*PGD_2*) and leukotriene C_4 (*LTC_4*). *TNF*, tumor necrosis factor.

also contributes to the generation of Ca^{++} and PKC signals. These signaling events lead to the three major responses:

- ***Degranulation***. Activated PKC phosphorylates the myosin light-chain component of actin-myosin complexes located beneath the plasma membrane, leading to disassembly of the complex. This allows cytoplasmic granules to come in contact with the plasma membrane. The mast cell granule membrane then fuses with the plasma membrane, a process that is mediated by members of the SNARE protein family, which are involved in many other membrane fusion events. Different SNARE proteins present on the granule membranes and plasma membranes interact to form a multimeric complex that catalyzes fusion. The formation of SNARE complexes is regulated by several accessory molecules, including RAB3 guanosine triphosphatases and RAB-associated kinases and phosphatases. In resting mast cells, these enzymes inhibit mast cell granule membrane fusion with the plasma membrane. On FcεRI cross-linking, the resulting increase in cytoplasmic calcium concentrations and the activation of PKC block the activity of the inhibitory