Pro-resolving Lipid Mediators and Their Role in Inflammation

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Introduction

Overview of Inflammation

- A protective response that is essential for survival

<u>Causes of inflammation</u>

- Infections
- Physical or chemical injury
- Foreign bodies
- Immune reactions
- Ischemia
- Trauma

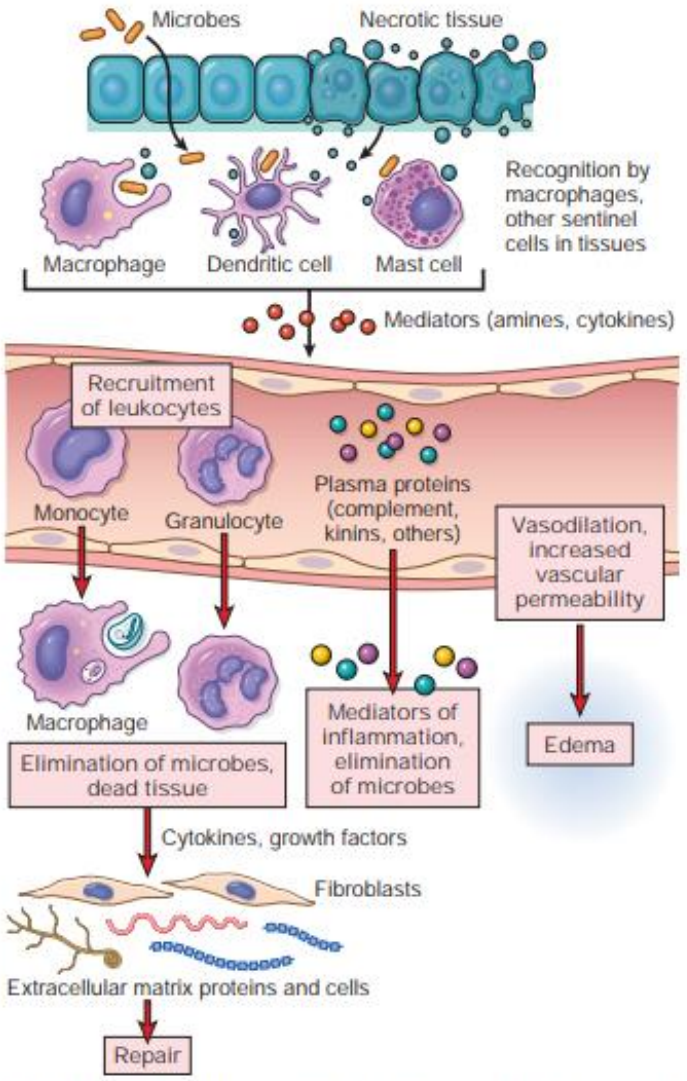


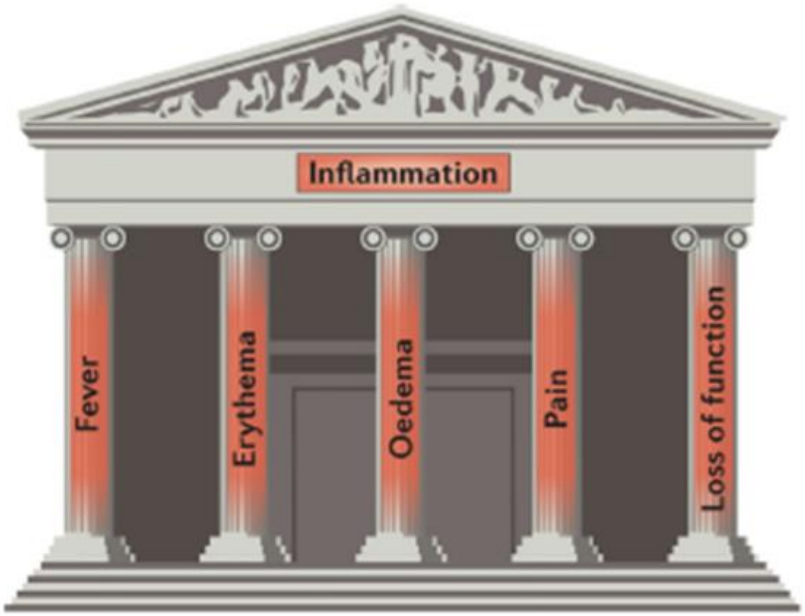
Figure 3-1 Sequence of events in an inflammatory reaction. Macrophages and other cells in tissues recognize microbes and damaged cells and liberate mediators, which trigger the vascular and cellular reactions of inflammation.

Robbins and Cotran, *Pathologic Basis of Disease* (2015)

Acute Inflammation

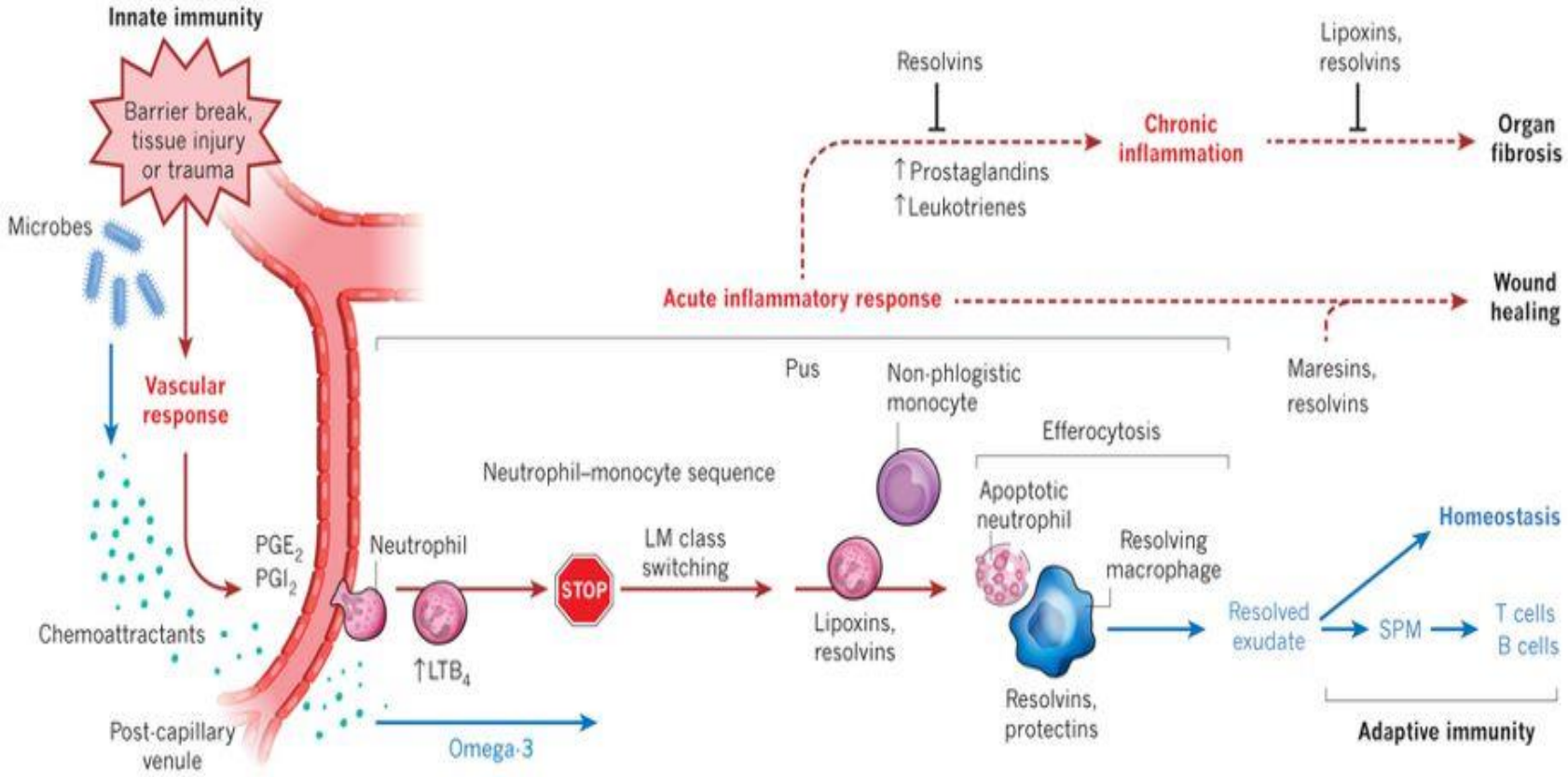
- Dilation of small vessels leading to an increase in blood flow.
- Increased permeability of the microvasculature enabling plasma proteins and leukocytes to leave the circulation.
- Emigration of the leukocytes from the microcirculation, their accumulation in the focus of injury, and their activation to eliminate the offending agent.

Cardinal Signs of Acute Inflammation



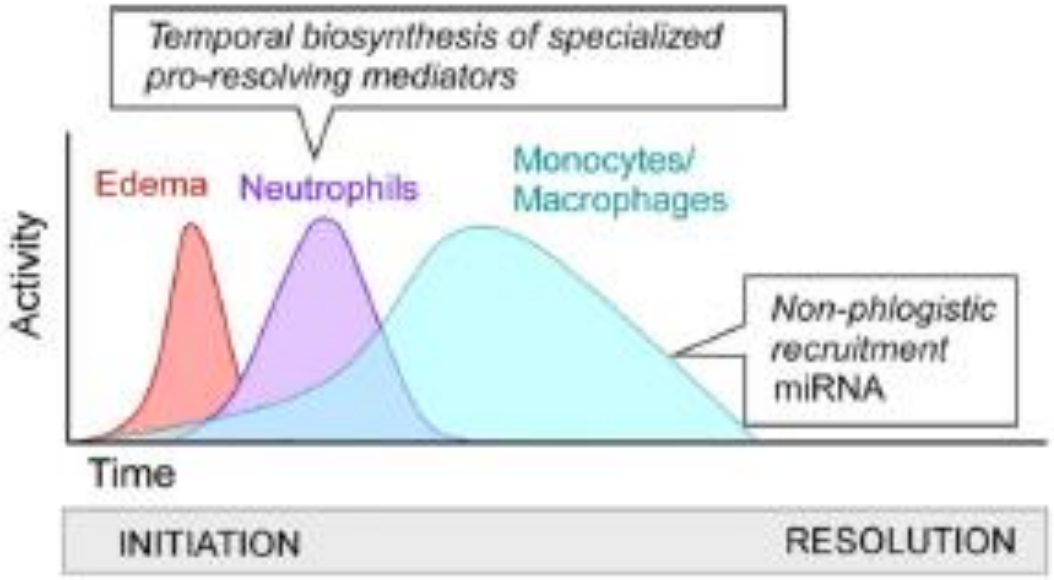
Basil et al. Nat Rev. Immunol. *2016*

Acute Inflammation



The role of lipid mediators in acute inflammation and resolution (Serhan et al. *2014*)

Acute Inflammation



Serhan et al. *2014*

Outcomes of Acute Inflammation

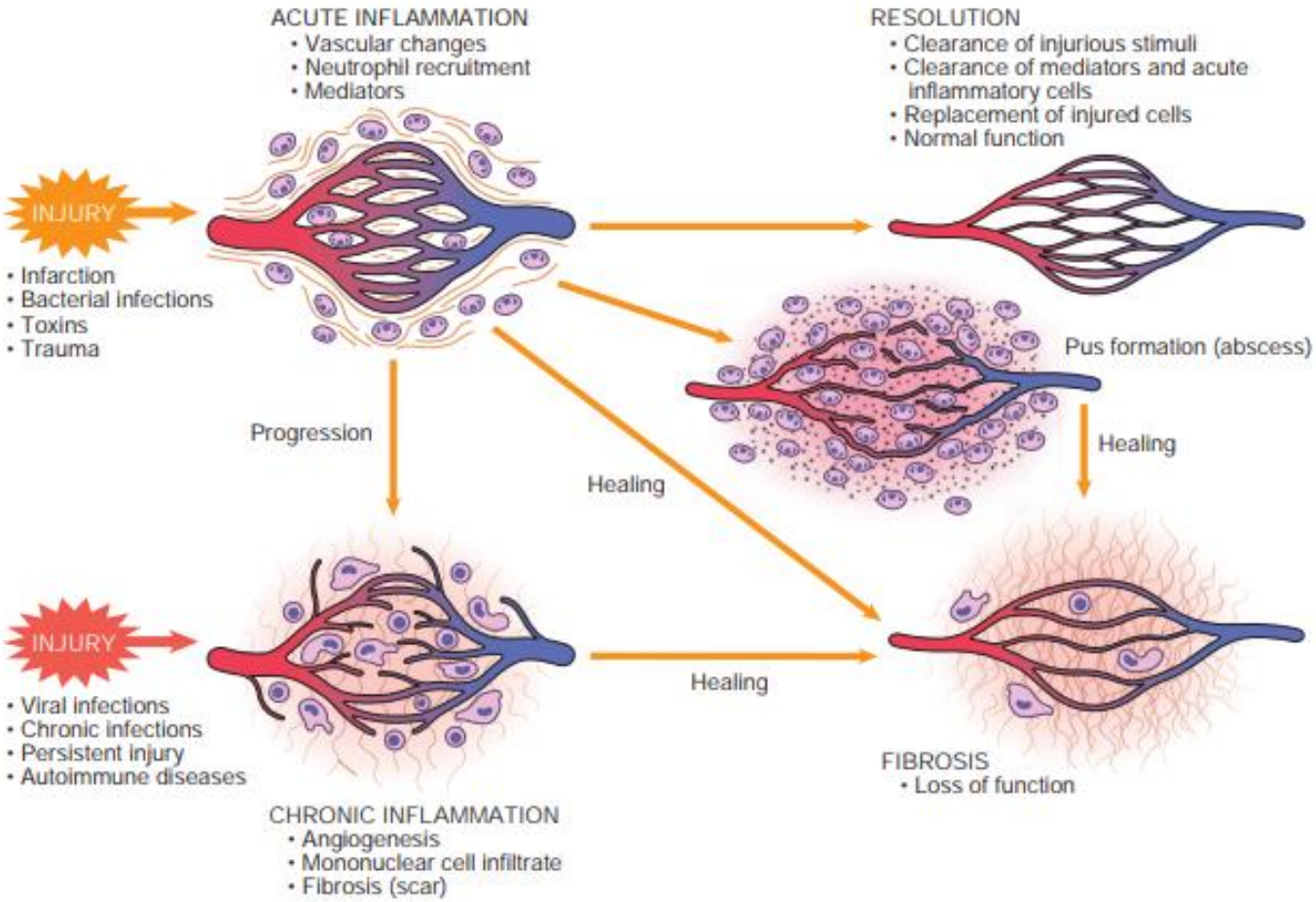


Figure 3-17 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic inflammation. The components of the various reactions and their functional outcomes are listed.

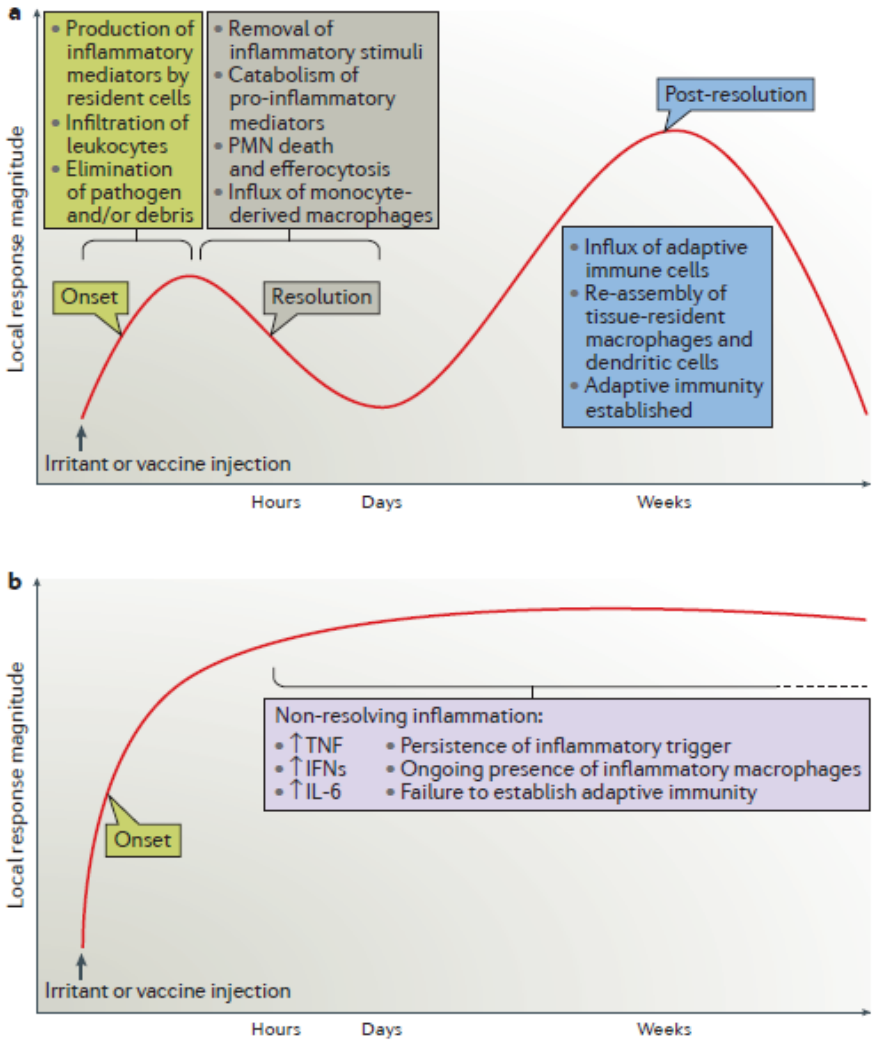
Chronic Inflammation

A response of prolonged duration (weeks or months) in which inflammation, tissue injury and attempts at repair coexist.

Characteristics:

- Infiltration with mononuclear cells, which include macrophages, lymphocytes, and plasma cells.
- Tissue destruction, induced by the persistent offending agent or by the inflammatory cells.
- Attempts at healing (angiogenesis and fibrosis).
- Mediated by cytokines produced by macrophages and lymphocytes (notably T lymphocytes).

Acute vs. Chronic Inflammation



Fullerton et. al *2016*

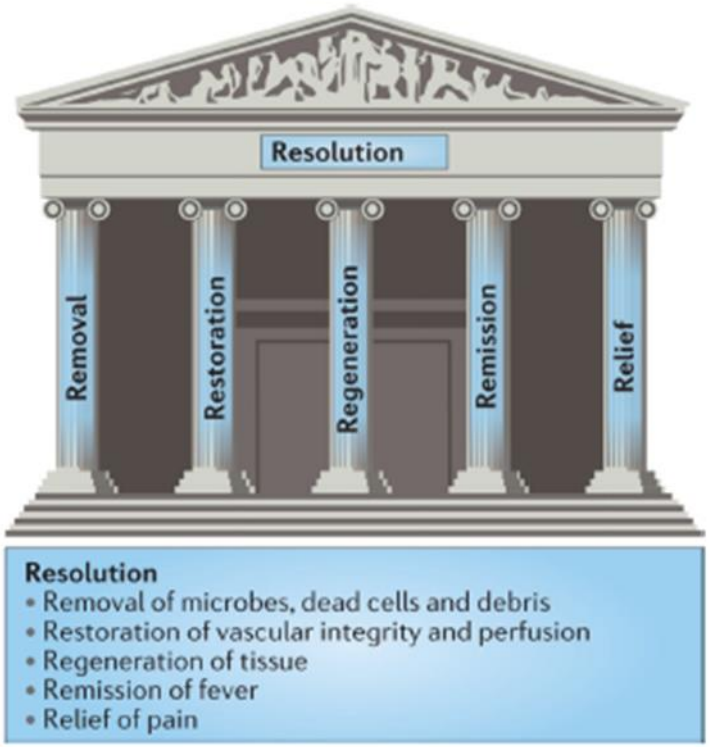
Acute vs. Chronic Inflammation

FEATURE	ACUTE INFLAMMATION	CHRONIC INFLAMMATION
Pathogenesis	Microbial pathogens, trauma, burns	Persistent acute inflammation, foreign bodies (e.g., silicone, glass), autoimmune disease, certain types of infection (e.g., tuberculosis, leprosy)
Primary cells involved	Neutrophils	Monocytes/macrophages (key cells), B and T lymphocytes, plasma cells, fibroblasts
Primary mediators	Histamine (key mediator), prostaglandins, leukotrienes	Cytokines (e.g., IL-1), growth factors
Necrosis	Present	Less prominent
Scar tissue	Absent	Present
Onset	Immediate	Delayed
Duration	Few days	Weeks, months, years
Outcome	Complete resolution, progression to chronic inflammation, abscess formation	Scar tissue formation, disability, amyloidosis (refer to Chapter 3)
Main immunoglobulin	IgM	IgG
Serum protein electrophoresis effect	Mild hypoalbuminemia	Polyclonal gammopathy; greater degree of hypoalbuminemia
Peripheral blood leukocyte response	Neutrophilic leukocytosis	Monocytosis

Goljan et al. *2009*

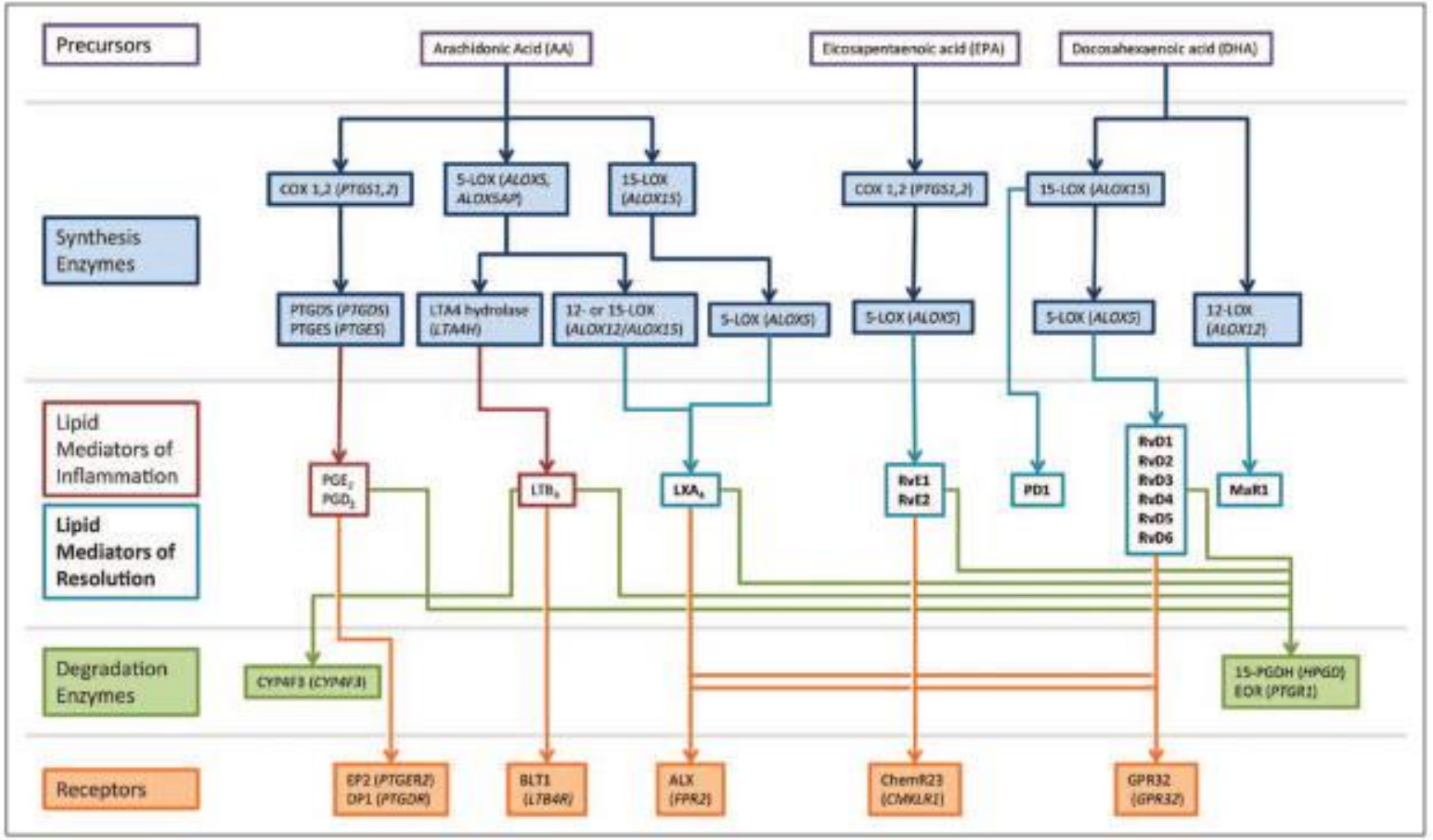
Resolution

- “Clean up” phase after the initial inflammatory response.
- An active biochemical process that involves the interaction of many mediators.



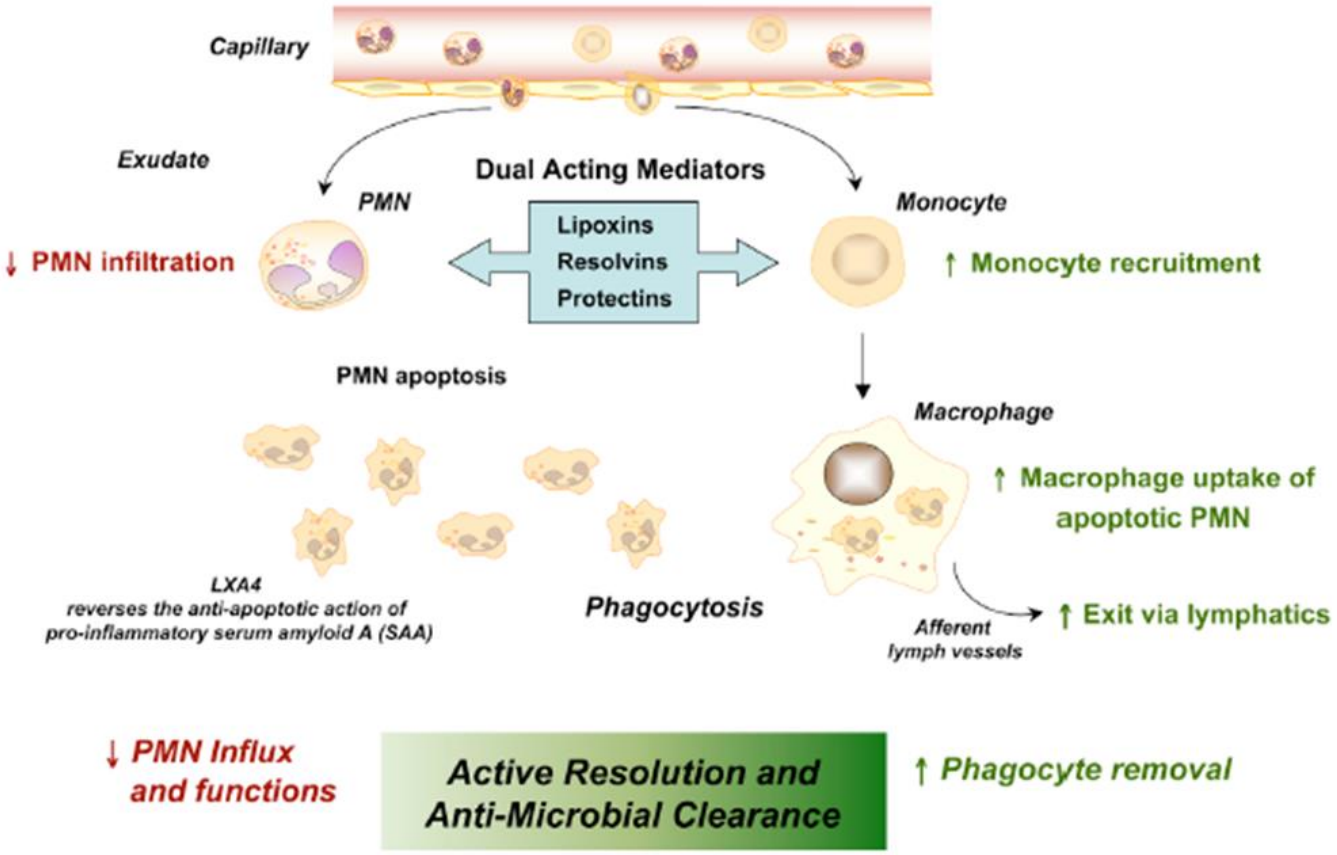
Basil et al. Nat Rev. Immunol. *2016*

Lipid mediators



Orr et al. *2016*

Dual anti-inflammatory and pro-resolution actions of specific lipoxins, resolvins and protectins



Serhan et al. *2014*

Cell-type specific actions of pro-resolving lipid mediators

Mediator	Target cell	Action(s)
Lipoxin A_4	Neutrophil	Inhibits chemotaxis, *trans*-endothelial and *trans*-epithelial migration
		Inhibits neutrophil–epithelial cell interactions
		Inhibits superoxide anion generation and degranulation
	Monocyte	Stimulates chemotaxis and adhesion
		Inhibits peroxynitrite generation
		Reduces IL-8 release by cells from individuals with asthma
	Macrophage	Increases engulfment of apoptotic neutrophils
	Eosinophil	Inhibits migration and chemotaxis
		Inhibits generation of eotaxin and IL-5
	NK cell	Inhibits NK cell cytotoxicity
		Increases granulocyte apoptosis
	ILC2	Inhibits IL-13 release
	Dendritic cell	Inhibits IL-12 production
	Epithelial cell	Increases proliferation after acid injury, blocks IL-6 and IL-8 release
	Endothelial cell	Stimulates PKC-dependent prostacyclin formation
		Blocks the generation of reactive oxygen species
		Inhibits VEGF-induced endothelial-cell migration
	Fibroblast	Inhibits IL-1β-induced IL-6, IL-8 and MMP3 production
		Inhibits CTGF-induced proliferation
	Smooth muscle	Inhibits LTC_4-initiated migration

Serhan et al. *2014*

Cell-type specific actions of pro-resolving lipid mediators

Mediators	Cell type	Action(s)
Protectin D1	Neutrophil	Upregulates CCR5 expression[73]
	Macrophage	Stimulates nonphlogistic phagocytosis of apoptotic neutrophils[15]
	T cell	Inhibits TNF and IFNγ secretion, promotes apoptosis[71]
		Upregulates CCR5 expression[73]
	Microglia	Inhibits IL-1β expression[11]
	Epithelia	Protects from oxidative-stress-induced apoptosis in retinal pigment epithelia[70]
Resolvin E1	Neutrophil	Stops transepithelial and transendothelial migration[9]
	Macrophage	Stimulates nonphlogistic phagocytosis of apoptotic neutrophils[15]
	Dendritic cell	Blocks IL-12 production[58]
	T-cell	Upregulates CCR5 expression[73]
Resolvin D1	Microglia	Inhibits IL-1β expression[10]
Aspirin-triggered resolvin D1	Neutrophil	Stops transmigration[10, 67]

Serhan et al. *2014*

Pro-resolving Lipid Mediators in Disease

Graft versus host disease	Lipoxins	LXA_4 and 15-epi-LXA_4 administration improves clinical symptoms
Alzheimer disease	Lipoxins	LXA_4 decreases NF-κB expression and recruits microglia, promoting clearance of amyloid-β deposits and improving cognition in mouse models
	Protectins	NPD1 promotes brain cell survival and an anti-apoptotic gene expression programme in human tissue
	Resolvins	RvD1 stimulates macrophage phagocytosis of amyloid-β *in vitro* in PBMCs from patients with Alzheimer disease
Amyotrophic lateral sclerosis	Resolvins	RvD1 inhibits IL-6 and TNF production in macrophages derived from post mortem samples
Murine models of inflammatory bowel disease or colitis	Lipoxins	15-epi-LXA_4 enhances phagocytic clearance of bacteria and limits the inflammatory cytokine milieu
		LXA_4, through NF-κB, downregulates pro-inflammatory cytokines and improves mortality
	Resolvins	RvE1 suppresses pro-inflammatory response of macrophages
		RvE1 blocks leukocyte inflammation and protects against colitis
		RvD2 and AT-RvD1 decrease neutrophil infiltration and cytokine response, and improves clinical metrics
Diabetes	Resolvins	RvD1 improves glucose tolerance and insulin sensitivity associated with obesity-induced diabetes in mice
		The RvD1 precursor 17-HDHA reduces adipose tissue inflammation and improves glucose tolerance in mouse models
Chronic pancreatitis	Resolvins	RvD1 limits inflammation in the dorsal horn, limiting allodynia in rat models

Serhan et al. *2014*

My Diploma Thesis

The aim of my diploma thesis:

Pro-resolving lipid mediators in the secretome of peripheral blood mononuclear cells.

What results do we expect?

Time-dependent secretion of resolvins D1-D4, resolvin E1, maresin 1, protectin.

Methodology:

ELISAs

Conclusion

- Resolution is an active process.
- Pro-resolving lipid mediators play a key role in the resolution of inflammation.
- Pro-resolving lipid mediators are involved in the mechanism of many diseases.

Thank you for listening!