Chapter 2
Inflammation and Pain

Jasmine Ji, Matthew Yuan, and Ru-Rong Ji

Abstract Inflammation is the body's natural response to injury or the infiltration of a foreign substance. The process is defined by five cardinal signs: redness, heat, swelling, loss of function, and pain. Because of its relationship with pain and injury, various treatments for inflammation have been historically documented. During inflammation, pro-inflammatory mediators can be produced by infiltrating and resident immune cells. These pro-inflammatory mediators can induce pain. On the other hand, recent evidence suggests that inflammation also resolves pain by generating anti-inflammatory and pro-resolving mediators. The inflammatory process, when properly mediated via cellular mechanisms, eliminates pathogens and damaged or dead cells from the body. Thus, inflammation was proposed to resolve pain by producing specialized pro-resolving mediators (SPMs), derived from omega-3 unsaturated fatty acids. However, dysregulated inflammation, such as chronic inflammation, can lead to various pathological conditions associated with chronic pain. While acute pain, which is temporary and serves a protective purpose, is beneficial, chronic pain has no such protective purpose and severely degrades the quality of life of patients.

Keywords Acute inflammation · Acute pain · Anti-inflammatory mediators · Chronic inflammation · Chronic pain · COVID-19 · Infection · Inflammatory mediators · Specialized pro-resolving mediators (SPMs) · Resolution of inflammation

J. Ji (✉)
Wellesley College, Boston, MA, USA
e-mail: jj101@wellesley.edu

M. Yuan
Center for Translational Pain Medicine, Department of Anesthesiology, Duke University, Durham, NC, USA

R.-R. Ji
Center for Translational Pain Medicine, Department of Anesthesiology, Duke University, Durham, NC, USA

Departments of Cell Biology and Neurobiology, Duke University, Durham, NC, USA

R.-R. Ji et al. (eds.), *Neuroimmune Interactions in Pain*,
https://doi.org/10.1007/978-3-031-29231-6_2

2.1 What Is Inflammation?

Inflammation is the body's response to infection and damage to tissues, with the end goal of eliminating any foreign pathogens and repairing any tissue damage. Inflammatory stimuli can be broadly viewed as anything that causes infection (e.g., viruses, bacteria, microbes, other pathogens) or tissue damage (e.g., physical trauma, toxic chemicals, radiation) (Medzhitov 2008). In response to an inflammatory stimulus, the body will initiate an inflammatory response; this response typically involves the recognition of the stimulus via cell surface pattern receptors, the release of inflammatory mediators that subsequently activate inflammatory pathways, and the release of inflammatory markers that lead to the recruitment of inflammatory cells (Ji et al. 2016). Once foreign pathogens have been eliminated and the tissues have been repaired, the inflammatory response will have served its purpose and be subsequently resolved. In some cases, however, the inflammatory response may not be properly mediated, morphing into a chronic process; unlike its helpful, acute counterpart, chronic inflammation is harmful to the body, and, indeed, a cause and symptom of various inflammatory diseases (Donnelly et al. 2020; Medzhitov 2008). Chronic inflammation is also often closely associated with chronic pain (although notably there are also several painless or partially painless chronic inflammatory conditions) (Ji et al. 2014, 2018; Lewis et al. 2020; Martinez Quintero et al. 2021). Inflammation can be broadly divided into neurogenic inflammation and neuroinflammation, based on the type of pathological pain it underlies (Chiu et al. 2012; Ji et al. 2014, 2018; Matsuda et al. 2019). The following chapter will consider the cardinal signs of inflammation, its history, the biological processes involved in inflammation, the close correlation between pain and inflammation, and the implications of chronic inflammation.

2.2 A History of Inflammation

The existence of inflammation has been known for millennia (Fig. 2.1), described early on in the medical texts of the ancient Greeks and Egyptians. This is no wonder, as the condition is easily observable, chaperoning injuries and infections, often lethal in ancient times. The Greek physician Hippocrates described signs of inflammation in the fifth century, using terms such as *oidēma* (swelling), which we today call edema. He also seemed to appreciate the role of inflammation in the healing process following injury. The first four cardinal signs—redness, swelling, heat, and pain—were described by the fifth-century Roman writer Aulus Cornelius Celsus, in the oft-quoted phrase, "calore et tumor cum calore et dolore" (redness and swelling with heat and pain), from his medical treatise, *De Medicina*, written during the first century (Plytycz and Seljelid 2003).

The next major advancement in understanding inflammation came much later, with British neurophysiologist Augustus Waller (1846) and German pathologist

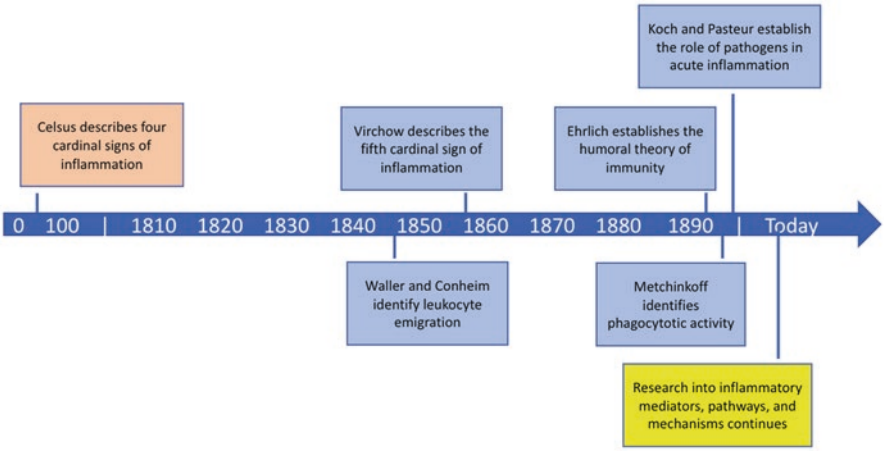

Fig. 2.1 Major events that led to our modern understanding of inflammation

Julius Cohnheim (1867). Both scientists independently described the emigration of leukocytes from blood vessels, as well as other vascular structures, during an acute inflammatory response. Using a microscope, they were able to observe the vasodilation, plasma leakage, and the movement of leukocytes from the blood vessels into neighboring tissue. In other words, they were able to identify some of the most critical events that occur during the inflammatory process (Rochae e Silva 1978).

In 1858, Rudolph Virchow, the German physicist often known as the "father of modern pathology," described the fifth cardinal sign of inflammation in his book *Cellularpathologie*: disturbance of function. This final sign differs from the previous four in that it is the only sign that appears in all inflammatory processes, not just in acute processes like the previous four. Virchow's work also established the concept that pathologies arise from cells and not the four humors, as was previously believed (Heidland et al. 2006).

In 1892, there came the discovery of phagocytes and phagocytosis by Russian zoologist Élie Metchnikoff, who was awarded a Nobel Prize for his discovery. The theory of cellular immunity, which states that cellular immunity is based on the activity of phagocytes, followed. This theory emphasized the importance of macrophages and neutrophils in defending and maintaining the homeostasis of tissues (Plytycz and Seljelid 2003).

In 1890, German physiologist Emil von Behring and Japanese bacteriologist Shibasaburo Kitasato co-authored a paper describing the production of "antitoxins" against diphtheria and tetanus toxins, one of the earliest examples of serum therapy (Plytycz and Seljelid 2003). Their paper inspired German physician Paul Ehrlich's humoral theory of immunity, also known as antibody-mediated immunity, which describes the ability of B-cells, a type of immune cell, to produce antibodies, large proteins that respond to and counteract antigens, proteins found on many pathogens (Rochae e Silva 1978). Belgian immunologist Jules Bordet followed-up in 1896

with his work examining the role of serum components in immunity. German physician Robert Koch and French microbiologist Louis Pasteur contributed greatly to the modern understanding of inflammation by specifying microbial agents as a major inducer of the acute inflammatory response (Rochae e Silva 1978).

Today, the study of inflammation accelerates and expands as researchers probe the different classes of inflammatory mediators, discover the cells and pathways that regulate their production, and reveal their mechanisms of action. We now understand that inflammation has many different forms, and can be induced, regulated, and resolved in multiple different ways. As modern medicine becomes increasingly effective at resolving acute inflammation and increasing lifespan, chronic inflammation has emerged as the next great topic of interest. Inflammatory conditions, driven by chronic inflammation, plague many people, especially in old age. These conditions include atherosclerosis, asthma, type 2 diabetes, neurodegenerative diseases (e.g., Alzheimer's disease), and cancer. Studying inflammation would provide insights into these debilitating and widespread conditions (Scrivo et al. 2011).

A PubMed search shows that doctors were interested in inflammation as early as 1791 (though PubMed itself was only founded in January of 1996; Fig. 2.2a) when Mr. Thomas Mainwaring, a doctor, wrote a letter to his patient who had been attacked and subsequently suffered from severe inflammation in his throat (Mainwaring 1791). Up until 1970, inflammation research remained relatively rare until the development of endothelial cell research in the 1970s, which quickly exploded, contributing greatly to inflammatory research due to the enormous role that endothelial cells play in inflammation. Aided by endothelial cell research, the number of papers on inflammation has grown exponentially in the past 50 years. Development of gene-targeted knockout technology has allowed scientists to study the roles of various immune-cell-derived mediators, such as cytokines and chemokines (small cytokines), and endothelial-cell-derived adhesion molecules, as well as their receptors in inflammation. These studies have helped scientists create useful models of inflammation. Further methodologies developed in immunology, including antibody blocking, in mice have also contributed significantly to the progress of inflammation research (Kvietys and Granger 1997). Since 2000, the number of papers on inflammation has increased steadily every year, showing the lingering relevance and importance of inflammation in our lives (Fig. 2.2a). Correlation with inflammation has been demonstrated in almost all types of human diseases.

2.3 Inflammation and Pain

2.3.1 The Correlation Between Inflammation and Pain: Clinical Relevance and Social Impact

Inflammation and pain are two closely interrelated concepts that often go hand in hand in research (Calvo et al. 2012; Ji et al. 2016; Fig. 2.2b). It is of critical importance to investigate their correlation and interactions not only in acute pain

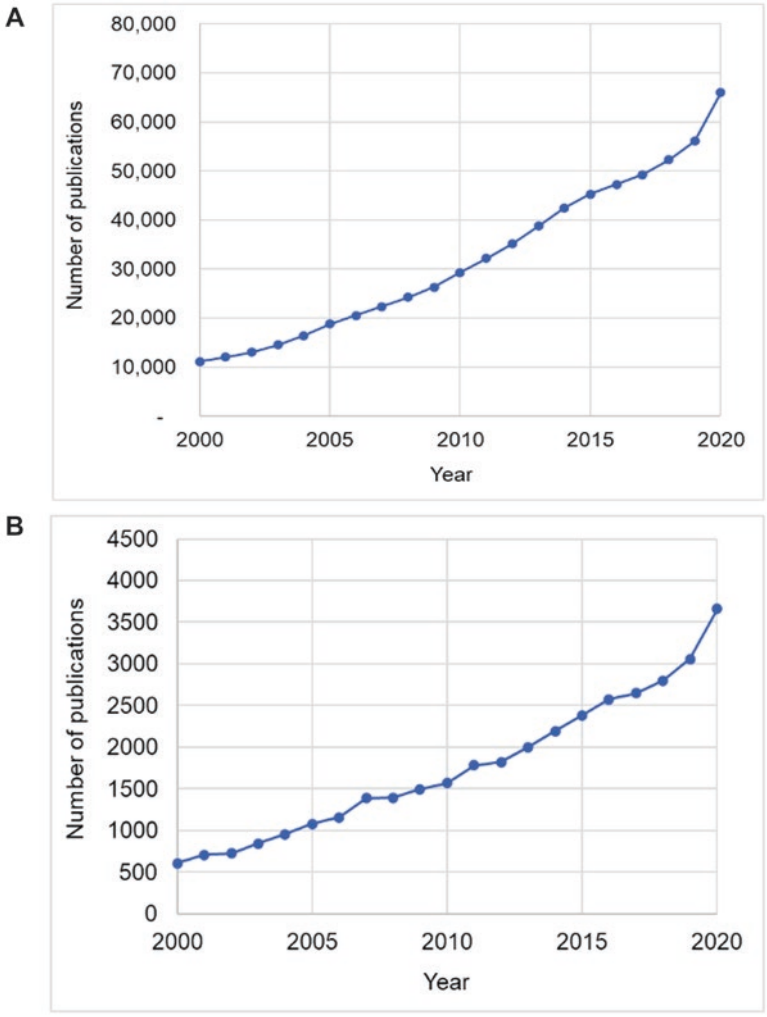

Fig. 2.2 A PubMed search shows (**a**) an increasing number of publications using the keyword "inflammation" over the last two decades and (**b**) an increasing number of publications using the keywords "inflammation" and "pain" over the last two decades

conditions but also in chronic pain conditions. Chronic pain conditions plague tens of millions of Americans, with annual costs on pain management and labor loss exceeding 600 billion US dollars per year (Gereau et al. 2014). Inflammation-associated pain is typically treated with local anesthetics, opioids, and non-steroidal anti-inflammatory drugs (NSAIDs). Each of these has obvious problems, however (Brigham et al. 2021). Opioids function by blocking pain signals in the spinal cord and brain (Corder et al. 2018). Thus, people treated with opioids are temporarily completely incapable of feeling pain. Local anesthetics work similarly; by binding

to the sodium channels, they prevent sodium ions from entering, in turn preventing nerve signals from being conducted to the brain. Being completely incapable of feeling pain is dangerous. Acute pain exists as a protective mechanism—to prevent you from reaching into a hot oven without mitts, or to encourage you to take immediate action after dropping your textbooks on your foot, for example. Thus, blocking pain signals is hardly an ideal solution. Addiction is also a problem, which can lead to breathing suppression and subsequently death. Opioid abuse, in particular, is an enormous problem that has led to America's Opioid Crisis. The third treatment option, NSAIDs, does not block pain signals. Instead, NSAIDs block enzymes like cyclooxygenases (Cox-1 and Cox-2), which produce prostaglandins (e.g., PGE2), lipids that promote swelling and pain in inflammation. While NSAIDs are effective in treating acute inflammatory pain and headache, they have their own issues; they can damage your stomach lining and even result in internal bleeding (Brigham et al. 2021).

Lack of effective treatments for chronic pain is associated with the ongoing crisis of opioid use disorder (OUD) (Volkow and Collins 2017). In 2020, more than 92,000 Americans died from drug overdoses, a nearly 30% increase over 2019, according to a report from the Centers for Disease Control and Prevention. Thus, there is an urgent need to develop non-opioid medicine that can control excessive inflammation and neuroinflammation for the prevention and resolution of chronic pain (Ji et al. 2018).

Though pain and inflammation often co-exist, some inflammatory conditions, especially chronic inflammatory conditions, may not involve pain (Fig. 2.3). Periodontal disease refers to a severe gum infection that can result in inflammation of the gums, as evidenced by their red, tender, and swollen appearance. Notably periodontal disease is frequently painless, either during early stages or throughout the entire process. Atherosclerosis occurs due to the build-up of fats, cholesterol, and other substances in and on the artery walls, which obstruct blood flow and can rupture, causing acute occlusion of the artery by clotting. Despite chronic inflammation of the artery walls, this condition has no obvious painful symptoms, until a build-up becomes severe enough to block blood flow. Asthma is a rather common condition, in which inflamed airways cause additional mucus to be produced, which interferes with breathing. Asthma can cause wheezing, which forces the chest to constrict and produces chest pain. Even so, the actual location of inflammation, the lungs, does not experience pain. Lastly, early-stage melanoma, alongside some other early-stage cancers, also is not painful. Interestingly, melanoma cells produce specific mediators called immune checkpoint inhibitors that can suppress pain (Chen et al. 2017a). This lack of pain is especially misleading, as patients cannot be aware of the cancer in an earlier stage and take necessary precautions. These painless inflammatory conditions present two facts: the first is that inflammation does not necessarily induce pain, despite drastic tumor growth that causes significant skin lesion; the second is that inflammation without pain can be quite dangerous, as pain serves as a warning sign. It is noteworthy that many types of cancers are diagnosed by doctors after patients have reported pain.

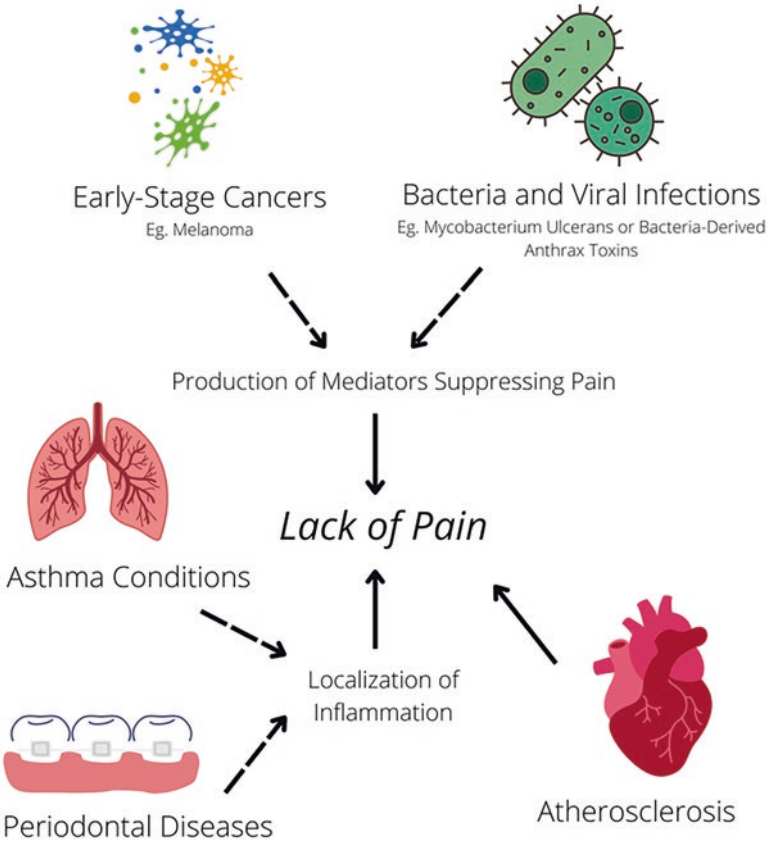

Fig. 2.3 There are also painless inflammatory conditions due to the production of anti-nociceptive mediators at the inflammatory sites

Bacterial and viral infections are typically painful (Chiu 2018; Chiu et al. 2013), but are not always painful (Ji et al. 2016). For example, *Mycobacterium ulcerans*, the etiological agent of Buruli ulcer, produces extensive and severe skin lesions but not pain. Instead, *M. ulcerans* produces remarkable analgesia by producing analgesic mediators (Marion et al. 2014). Several types of viruses, such as herpes simplex virus (HSV) and varicella zoster virus (VZV), are capable of infecting sensory neurons and evoke severe pain. However, during reactivation of HSV, patients frequently experience paresthesia (numbness, tingling), signs of analgesia, prior to the development of acute pain following ulceration (Donnelly et al. 2020). Recently, it was found that bacteria-derived anthrax toxins produce potent pain inhibition by binding ANTXR2, the high-affinity receptor for anthrax toxins, which are expressed by nociceptors (Yang et al. 2021). Thus, infections can be both painful and non-painful (Donnelly et al. 2020) (Fig. 2.3).

2.4 The Inflammatory Process

Despite its inconveniences, inflammation is an enormously important process during which the body cleans up the pathogens and dead cells at the site of injury and begins the healing process. Acute inflammation is activated by resident immune cells already present in the involved tissue, mainly resident macrophages, dendritic cells, and mast cells. These cells have surface receptors called pattern recognition receptors (PRRs), which bind two kinds of molecules: pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). PAMPs are substances associated with various pathogens, but can still be distinguished from host molecules. DAMPs are substances associated with host-related injury and cell damage (Akira et al. 2006). In addition, PRRs are also activated by microbe-associated molecular patterns (MAMPs) (Boller and Felix 2009). When an infection, burn, or other injury occurs, these cells are activated (one of the PRRs recognizes a PAMP, DAMP, or MAMP) and release inflammatory mediators that result in the aforementioned cardinal signs of inflammation (Donnelly et al. 2020). Vasodilation and the resulting increase in blood flow cause redness and increased heat. Increased permeability of the blood vessels leads to the leakage of plasma proteins and fluid into the tissue in a condition known as edema, which then causes swelling. Different types of mediators that are released during this process, such as bradykinin, prostaglandins, cytokines, and chemokines, can cause pain or hyperalgesia (Gold and Gebhart 2010; Ji et al. 2014). Mediator molecules, such as chemokines (small cytokines), also change blood vessels to allow the migration of leukocytes, such as neutrophils and macrophages, out of the blood vessels into tissue in a process called extravasation. Plasma extravasation can also be induced by neuropeptides, such as substance P and calcitonin gene-related peptide (CGRP), released after stimulation of pain-sensing nerve fibers during neurogenic inflammation (Xanthos and Sandkuhler 2014). The neutrophils move along a chemotactic gradient (moving from an area of low chemical concentration to an area of high chemical concentration) made by local cells in order to reach the site of injury. The fifth cardinal sign of inflammation, loss of function, could be related to both injury and illness. For example, an inflamed joint cannot be moved properly due to acute injury or chronic diseases such as arthritis. Inflammation can make it difficult for patients to breathe due to a respiratory infection, which has been experienced by many COVID patients. Accumulating evidence suggests that PRRs such as toll-like receptors (TLRs) are also present in primary sensory neurons and play important roles in regulating neuronal activity and excitability and sensory functions such as pain and itch (Diogenes et al. 2011; Donnelly et al. 2020; Liu et al. 2010). Furthermore, neuronal TLR signaling in nociceptive neurons was shown to regulate local immunity (Liu et al. 2014). Thus, neuron–immune interactions may be involved in fundamental inflammatory processes.

Additionally, there are several biochemical cascades that do not involve cells. Instead, they consist of preformed plasma proteins that work together to start and spread the inflammatory response. These systems include the complement system,

which is activated by bacteria and the coagulation and fibrinolysis (breaking down fibrin) cascades, which are activated by necrosis (i.e., a burn or blow). Acute inflammation can be seen as the first line of defense against injury. Acute response to inflammation needs constant stimulation to persist. Inflammatory mediators last only temporarily; afterward, they are rapidly degraded in the tissue. It was generally believed that acute inflammation comes to a halt once the stimulus is removed. Recent progress has demonstrated that resolution of inflammation is not a passive process but an active process, which can generate specialized pro-resolution mediators (SPMs) that promote the resolution of inflammation, as well as pain (Ji et al. 2011; Serhan 2007). Below, we will be discussing some of the mechanisms of inflammatory mediators more in depth.

2.5 Cellular Mechanisms

Cellular mechanisms involve a number of different leukocytes, which carry out leukocyte extravasation and phagocytosis during inflammation to rid the body of any foreign substances (Fig. 2.4). Extravasation is the process leukocytes use to reach the site of injury. During this process, leukocytes, which are usually located at the center of blood vessels, will move toward the walls of the vessels. Activated macrophages in tissue will release cytokines including interleukin (IL)-1β and tumor necrosis factor (TNF)-α (or TNF, as this is the only member), which causes the production of chemokines that bind to proteoglycans (a major component in extracellular matrices). This forms a gradient in both the inflamed tissue and along the endothelial wall. Inflammatory cytokines then rapidly induce the expression of P-selectin (a cell adhesion molecule) on the surfaces of endothelial cells. P-selectin binds (albeit weakly) to carbohydrate ligands on leukocyte surfaces, moving across the endothelial surface during which bonds are made and broken. Injured cells will release cytokines that induce E-selectin (which functions similarly to P-selectin) expression on endothelial cells. Cytokines also induce integrin ligand, such as CADM-1 (cell adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule1) expression on endothelial cells, which control the adhesion of the selections and contribute to slowing leukocytes. The weakly bound leukocytes can then detach if they remain non-activated by chemokines produced in injured tissue following signal transduction through G-protein-coupled receptors (GPCRs). These receptors activate integrins on leukocytes, increasing the bound integrin receptor affinity for ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 on the endothelial cell surface, thus firmly binding the leukocytes to the endothelium. Once the leukocytes have been bound to the endothelium, they will transmigrate, or move across the endothelium in a process called diapedesis. In this process, also termed chemotaxis, chemokine gradients will cause the leukocytes to move in between adjacent endothelial cells. The endothelial cells in turn will retreat, allowing the leukocytes to move into surrounding tissue (Fig. 2.4). After the leukocytes have reached the tissue interstitium, they will bind to the extracellular matrix. A variety

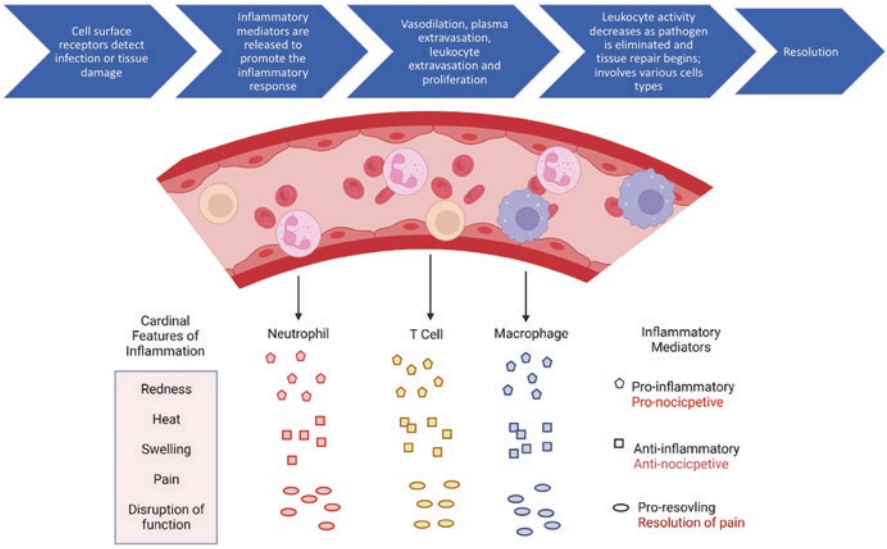

Fig. 2.4 Basic flowchart of the inflammatory process, induced by infection or tissue damage. Inflammation is associated with infiltration of immune cells, such as neutrophils, macrophages, and T-cells. Acute inflammation results in resolution and wound healing. There are five cardinal features of inflammation. After inflammation, immune cells produce pro-inflammatory mediators that are pro-nociceptive. Inflammation also produces anti-inflammatory and pro-resolving mediators that are anti-nociceptive and promote pain resolution

of chemoattractant (e.g., C3a or C5) will then guide the leukocytes along chemotactic gradients toward the inflammatory source.

Mounting evidence suggests that inflammation is also regulated by primary sensory neurons such as pain-sensing nociceptive neurons (nociceptors) (Talbot et al. 2016). Nociceptors include unmyelinated C-fiber neurons and myelinated Aδ-fiber neurons, with their cell bodies localized in dorsal root ganglion (DRG) and trigeminal ganglion (TG) and axons/terminals innervating the skin, muscle, and joint (Julius and Basbaum 2001; Woolf and Ma 2007). Upon activation, nociceptors release neuropeptides, cytokines, chemokines, and amino acids from their terminals that potently shape the function of innate and adaptive immune cells in the local environment (Baral et al. 2019; Liu et al. 2014). For some pathogens, neuron–immune interactions enhance host protection from infection, but for other pathogens, neuron–immune signaling pathways can be exploited to facilitate pathogen survival, depending on specific disease conditions, disease progression stages, and mediators released from nociceptors (Baral et al. 2019). For example, C-fiber nociceptors have been shown to activate dendritic cells and subsequent activation of T-cells, leading to the pathogenesis of psoriasis, a skin disease associated with autoimmune dysfunction and chronic itch, via the release of the neuropeptide CGRP (Riol-Blanco et al. 2014; Zhang and He 2020). On the other hand, recent study also

shows that activation of TRPV1 (transient receptor potential vanilloid 1) positive nociceptive neurons are sufficient for host defense against infections (Cohen et al. 2019; Lei et al. 2022).

The discovery of glial cells and neuroinflammation revolutionized how scientists understood chronic inflammation. Glial cells, immune cells found in the central nervous system (CNS), are key players in the process known as neuroinflammation, or inflammation of tissue in the peripheral nervous system (PNS) and CNS. Activation of glial cells, which include Schwann cells in peripheral nerves (e.g., sciatic nerve), satellite glial cells in the DRG and TG, and microglia, astrocytes, and oligodendrocytes in the spinal cord and brain, leads to the release of glial mediators that can modulate pain sensitivity (Gosselin et al. 2010; Hanani and Spray 2020; Ji et al. 2016). In other words, glia-produced neuromodulators can increase pain sensitivity in neuroinflammation, which in turn can sustain sensitization in nociceptive neurons. By maintaining signaling interactions between neurons and glial cells, neuroinflammation can thus modulate chronic pain (Ji et al. 2014). Please see more details in Chap. 5.

2.6 From Inflammation to Infection and Sterile Inflammation

2.6.1 From Inflammation to Infection

The inflammatory process described above is the standard reaction to inflammation by infection. Infection, it should be noted, is defined by the entrance of a foreign substance into the body, often through a wound, and can be broadly divided into four categories, including bacterial, viral, fungal, and prion. Inflammation to infection is a common form of inflammation, though it is actually not the only form of inflammation (Medzhitov 2010, 2021).

COVID-19, the respiratory condition caused by the coronavirus, is a notable example of an inflammatory condition. The virus causes severe inflammation in the lungs that can result in the excessive mucus production and, consequently, an inability to breathe. This excessive inflammation has been noted to cause damage to the alveoli of the lungs, which are responsible for the exchange of oxygen and carbon dioxide. Specifically, COVID-19 enters alveolar type II cells, through the receptor protein angiotensin-converting enzyme 2 (ACE2), which is found in the plasma membrane of cells, including human sensory neurons (Shiers et al. 2020). As the disease progresses, a mark of severity is demonstrated when the linings of the pleura, which are the tissue layers that surround the lungs, become irregular, caused by interstitial thickening and worsening inflammatory conditions.

2.6.2 *Sterile Inflammation*

During tissue damage, cells that die can cause an inflammatory response quite similar to infection-induced inflammation. Note that sterile injury and injury with infection are quite different, as injury with infection involves microbes. Most injuries are associated with infection, as they often involve breaking the skin, the first barrier of the body, which allows microbes to enter the body. More rarely, sterile inflammation will occur, during which cells are damaged or die in a sterile setting, most often due to ischemia (lack of blood supply to a particular body part), ischemia-reperfusion (tissue damage that occurs as blood returns to oxygen-deprived tissue due to ischemia), and trauma that can be found in the nerve, spinal cord, and brain. In these cases, inflammation occurs without infection, but still causes events such as neutrophil and monocyte infiltration, in addition to dendritic cell activation. In more severe cases, sterile inflammation can advance into circulatory shock or even multiple organ failure. Stunningly, how tissue injury without infection is detected is poorly understood, though TLRs and other innate receptors may play a role in discovering sterile injuries. One possibility, however, is that endogenous molecules that are released with cell death following necrosis may be a marker for sterile cell injury, including β-defensin, heat shock proteins, hyaluronan, uric acid crystals, as well as many other biomolecules, such as high-mobility group box protein 1 (HMGB1) and microRNAs (e.g., let-7b). Members of the TLR family are thought to be responsible for recognizing these molecules, such as activation of TLR4 by HMGB1 and activation of TLR7 by miRNA-let-7b (Liu et al. 2012), but it should be noted that relevant studies always run the risk of containing microbial contamination. Nonetheless, the capacity to stimulate inflammation of these endogenous molecules/ligands in response to microbial contamination is difficult to deny. Studies of TLR-deficient mice with various models of tissue injury are likely the best evidence for the fact that TLRs participate in detection of tissue injury. Various TLRs are not only expressed by immune cells, but also by glial cells, as well as neurons, such as DRG and TG neurons. TLRs play crucial roles in the pathogenesis of pain in animal models of inflammatory pain and nerve injury (Christianson et al. 2011; Donnelly et al. 2020; Liu et al. 2012). Please see more details in Chap. 8.

2.7 Tissue Injury, Microbes, and Pathogens: How Do They Affect the Host?

2.7.1 *Degrees of Inflammation: Tissue Injury and Pathogens*

We previously discussed the different types of inflammation and some mechanisms that cause them. However, it is also worthy to ask whether or not the severity of inflammation depends on the type of injury/infection. Do tissue injury, microbes, and pathogens cause different degrees of inflammation in the host?

Inflammation, if not induced or regulated properly, can cause enormous damage to the host. Though this inflammation is intended to protect the host, it also causes significant "collateral damage." A complex network of regulatory signals usually determines the degree of inflammation according to the original and the continuing cues. Inflammation signals have been described as "stop and go" signals, which play a role in determining when to escalate, dampen, or resolve an inflammatory response. Infection and injury, as discussed before, both cause inflammatory responses, but with different effects. The ligands responsible for signaling to them, however, converge on similar innate pathways. This seems to point to a lack of discrimination between qualitatively different stresses, which is rather confusing and requires further research. The existing complex feedback mechanisms suggest that there are additional mechanisms to address this, though, once again, very little is known. Pathogenic microbes, for example microbes with virulence mechanisms, seem to present a third qualitatively distinct challenge that requires an escalated response. It seems tempting to think that inflammation escalates or dampens based on the characteristics of the trigger, though specific gene induction downstream of innate receptors suggests that such a scenario may be plausible.

Does the host view tissue injury and microbial injury as different stresses? The extent to which the endogenous ligands produced during tissue damage stimulate the inflammatory signal induced by microbes remains unclear. It is possible that the responses to tissue damage and infection are similar, maybe due to the high likelihood of concomitant infection during tissue damage. Severe trauma as a method of sterile inflammation was mentioned above; sometimes, such trauma can lead to hemorrhagic shock, just as overwhelming infection can lead to sepsis. Nevertheless, these severe examples do not accurately represent if the overall purpose of each response is similar. It seems strange to think that the response to tissue damage would be the same to infection. The response to tissue damage has a purpose of healing, while the response to infection is first to rid the body of the infection and microbes. Tissue repair requires tissue remodeling, breakdown of extracellular matrix, and proliferation of cells to reestablish homeostasis. Many of these are also seen in the resolving phase of inflammation in response to infection, yet much of the collateral damage caused by activated neutrophils and macrophages during microbial infection might be unnecessary to heal a sterile wound. So far, research into the TLRs shows that an individual TLR is capable of differential signaling in response to different ligands, although the mechanisms responsible for these distinct responses are still unclear (Donnelly et al. 2020).

2.7.2 Gut Microbiota in Inflammation and Pain

Recent studies have pointed to a critical involvement of microbiota in health and disease. Microbiota include a range of microorganisms that may be commensal, symbiotic, or pathogenic found in and on all multicellular organisms, including bacteria, parasites, fungi, and viruses. Increasing evidence suggests microbiota play

a crucial role in regulating immunologic, hormonal, and metabolic homeostasis of their host, and gut–brain interaction is emerging as a hot topic in neuroscience and medicine (Erny et al. 2015). The recent progress in gut microbiota has expanded our knowledge on PAMPs. PAMPs are conserved microbial structures that are present in all microorganisms (including hot bacteria) and, thus, are not restricted to pathogens. Given our growing appreciation of the commensal microbiota (Erny et al. 2015), which activate the same host PRRs using the same ligands (e.g., lipopolysaccharide [LPS] and flagellin), it was suggested that these molecules should be renamed microbe-associated molecular patterns (MAMPs) (Donnelly et al. 2020). However, there should be functional distinction between MAMPs and PAMPs, as only the term PAMP emphasizes pathogenic microorganism, as opposed to MAMPs that focus on the commensal microbiota.

Emerging evidence has revealed an important role of microbiota in pain regulation. Microbiota have been implicated not only in visceral pain, but also in other types of pain including inflammatory pain, headache, and neuropathic pain, as well as opioid-induced anti-nociceptive tolerance (Guo et al. 2019). A study from Harvard Medical School has demonstrated that gut microbiota is critical for the induction of chemotherapy-induced pain, through LPS-mediated activation of TLR4 in the DRG (Shen et al. 2017). Furthermore, in the spinal cord and brain, gut-microbiota-derived mediators may regulate chronic pain and neuroinflammation through immune cells and microglia (Chen et al. 2018; Guo et al. 2019).

2.7.3 Antimalarial Drugs: Targeting Pathogens or Hosts?

According to the World Health Organization 2019 Report, malaria claims more than 400,000 lives every year. Artemisinin (ART) and its semisynthetic derivatives are used to treat malaria due to *Plasmodium falciparum* infection. Artemisia plants consist of 300 species and are distributed in temperate, warm temperate, and subtropical regions. Initial scientific efforts worldwide ended in failure after screening over 200,000 compounds against malaria. In the 1960s, Youyou Tu and her team screened over 2000 traditional Chinese recipes and made 380 herbal extracts, leading to the discovery of ART and its derivatives in 1972. This breakthrough in the twentieth-century tropical medicine has saved millions of lives in the world and led to the 2015 Nobel Prize in Physiology or Medicine. ART and its derivatives artemisinins (ARTs) might have a therapeutic value for several other diseases beyond malaria, including cancers, inflammatory diseases, and autoimmune disorders, as well as pain relief (Cao et al. 2020; Park 2019).

Malaria remains a major public health threat, especially in Southeast Asia, where artemisinin-based combination therapies (ACTs) are losing their efficacy (Wang et al. 2019). Artesunate (ARU) is a derivative of ART and the first-line treatment for children or adults with severe malaria. It was believed that the antimalarial

mechanism of action of ART is based on a direct action on parasites, involving activation of the endoperoxide bridge by ferrous heme. This reactive species may alkylate parasite proteins and lipids to cause lethality (Blasco et al. 2017). Recent studies have shown that ARU has an anti-inflammatory role in animal models, such as experimental cerebral malaria and experimental colitis, as well as human rheumatoid arthritis (RA) (An et al. 2017; Bang et al. 2021; Miranda et al. 2013; Xu et al. 2007; Yang et al. 2012). These studies suggest the possibility that the anti-malaria drugs may achieve their therapeutic effects by simultaneously targeting the pathogens (parasites) and treating the host (immune cells of the affected patients).

However, these studies failed to demonstrate the molecular targets (e.g., receptors) of ART and ARU on immune cells. Interestingly, it was proposed that in vivo ARU treatment causes rapid reduction in parasitemia by promoting phagocyte-mediated clearance (phagocytosis) of parasitized red blood cells (Khoury et al. 2017). Recent work from Duke University has identified a novel receptor for ARU and its anti-malaria actions (Bang et al. 2021). Computer simulations revealed ARU binding to GPR37, an orphan GPCR that was previously implicated in controlling macrophage phagocytosis (Bang et al. 2018). ARU promotes phagocytosis in macrophages in vitro and robustly improves survival and decreases hallmarks of sepsis, such as hypothermia, cytokine storm, and septic death.

The risk of death from sepsis is as high as 30% affecting about 49 million people worldwide in 2017, with 11 million deaths (Rudd et al. 2020). Thus, macrophage activation by GPR37 agonists such as ARU may also be of therapeutic benefit in sepsis. Notably, administration of ARU-primed macrophages was also sufficient to mitigate sepsis (Bang et al. 2021).

Infections of certain bacteria, such as *Staphylococcus aureus* and *Listeria* bacteria, result in severe pain in mice (Bang et al. 2021; Chiu et al. 2013). Intriguingly, *Listeria* bacteria-induced pain can be rapidly suppressed by ARU within 1 h of treatment. The severity and duration of the infection-induced pain are enhanced in mice lacking GPR37 (Bang et al. 2021). Furthermore, treatment of the infected animals with the ARU-stimulated macrophages could promote pain resolution (Bang et al. 2021). These findings strongly suggest that ARU-mediated activation of GPR37 in macrophages promotes pain resolution after infection, in further support of the emerging evidence showing the important role of macrophages in the resolution of inflammation and pain (Chen et al. 2020; Ji et al. 2011; Niehaus et al. 2021).

Last but not least, emerging studies suggest that ARU and/or its derivatives could inhibit SARS-CoV2 replication in vitro (Gendrot et al. 2020), leading to clinical evaluation of ARU in patients with mild COVID-19 (Kapepula et al. 2020). It will be of great interest and critical importance to investigate whether ARU may produce protective effects on COVID-19 through modulation of immune cells such as macrophages.

2.8 Inflammation Throughout the Body

Inflammation has long been recognized as a major cause of disease. An estimated 15% of human cancers are associated with chronic infection and inflammation. Acute and chronic tissue injury arising from inflammation has been found in many organ systems, including the heart, pancreas, liver, kidney, lung, and brain (Chen et al. 2017b).

Cardiovascular disease, and its associated pathology, atherosclerosis, is a major cause of death and disability throughout the world, and 23.6 million people are projected to die annually from cardiovascular disorders by 2030. Naturally, inflammatory mediators play very important roles in atherosclerosis, beginning with leukocyte recruitment and ending with the rupturing of the atherosclerotic plaque. Inflammation also contributes to cardiac stress. Increased levels of inflammatory cytokine and chemokine production and release are regularly found in affected cardiac tissues.

Pancreatitis, an inflammatory disease of the pancreas, has various causes, including the obstruction of the pancreatic duct, a mutation in the trypsinogen gene, or alcoholism. Acute pancreatitis (AP) occurs in 4–45 out of 100,000 patients per year and increases every year by approximately 1.3–4.0% in most developed countries. AP is one of the most common gastrointestinal-related causes for hospitalization in the USA. Chronic pancreatitis (CP) is less common than AP; however, CP patients suffer from chronic abdominal pain and exocrine and/or endocrine insufficiency, resulting in a reduced quality of life. Acinar cell destruction and activation of inflammatory cells, including macrophages, neutrophils, and granulocytes, which secrete inflammatory cytokines, are all seen in pancreatitis. Notably, pancreatitis is very painful, and pancreatic cancer is one of the most severe conditions of pain. Recent research has suggested that seeking surgery treatment early, among patients where surgical intervention is recommended, provides improved quality of life through more resistant pain relief (Skube and Beilman 2018).

Inflammation usually protects the liver from infection and injury, but excessive inflammation can cause extensive loss of hepatocytes, ischemia-reperfusion injury, metabolic alterations, and can eventually cause permanent hepatic damage. Inflammation can destroy hepatic parenchymal cells, increasing the risk of chronic liver diseases, such as non-alcoholic fatty liver disease (NAFLD) or viral hepatitis, which are a major cause of morbidity and mortality in the USA. Hepatocellular carcinomas, which make up 70–95% of all liver tumors, are known to cause abdominal pain in some patients and may cause intense abdominal pain in later stages in some patients (Christian-Miller and Frenette 2018).

Lung inflammatory diseases involve complex interactions between cells of the lungs and immune cells. Lung inflammation results primarily from tissue exposure to bacterial and viral pathogens, and/or environmental pollutants. Too much acute inflammation and resulting lung injury can cause pulmonary fibrosis and make gas exchange difficult. Unresolved lung injury and chronic inflammation are often seen

in acute respiratory distress syndrome, cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma. About 90% of COPD cases are associated with cigarette-smoking-induced inflammation in small airways and lung parenchyma. Smoking cigarettes is a major risk factor for COPD, which involves both systemic and pulmonary inflammation. COVID-19 is a respiratory condition that often features excessive inflammation and leukocyte dysfunction caused by the coronavirus. Severe COVID-19 can result in acute respiratory distress syndrome. Patients with severe COVID-19 are known to have alveolar damage. In addition, post-mortem samples often reveal lung lesions (Shi et al. 2020). Body aches (including chest pain), headaches, and muscle pains may be an early symptom of COVID-19. COVID-19-associated persistent chest pain is listed as an emergency symptom by Centers for Disease Control and Prevention (CDC) and requires urgent medical care.

Inflammatory responses occur in the brain in many CNS diseases, including autoimmune diseases, neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD), and epilepsy. Inflammation in the brain can increase the excitability of neurons, injure cells, and increase blood-brain-barrier permeability to various molecules. CNS diseases associated with neuroinflammation are caused by the activation of the brain's resident immune cells and microglia, which produce pro-inflammatory mediators (Ji et al. 2014, 2018). These neuroinflammatory processes also involve both the innate and adaptive immune systems and may resemble immune responses to systemic infection (Chen et al. 2017a). Notably, neuroinflammation is a driving force of chronic pain (Ji et al. 2014).

2.9 Pain in Autoimmune and Inflammation-Related Diseases

We will discuss painful systemic autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), neuromyelitis optica spectrum disorder (NMOSD), and multiple sclerosis (MS) (Lee et al. 2021), as well as inflammation-associated vascular diseases such as Erythromelalgia (Waxman and Dib-Hajj 2005).

2.9.1 Complex Regional Pain Syndrome (CRPS)

Autoinflammatory and autoimmune contributions to CRPS have been documented (Clark et al. 2018). CRPS typically develops after injury or surgery to a limb, and severe pain and disability are common. Human studies have revealed changes in cytokines and other inflammatory mediators in the skin of affected limbs. CRPS research has been facilitated by the development of animal bone fracture models that can mimic chronic pain lasting for several months (Wei et al. 2016). The

autoinflammatory components of CRPS are regulated by neuropeptide-containing peripheral nerve fibers and the sympathetic nervous system (Li et al. 2009). Pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α are identified in the peripheral tissues (e.g., skin) during the acute phases of the syndrome. Interestingly, IL-1β in the spinal cord also contributes to the maintenance of pain in the late-phase (Wei et al. 2016). Emerging evidence from human, animal, and translational studies has demonstrated the production of autoantibodies and the potential targets of those antibodies (Clark et al. 2018). Autoimmunity in skin and muscle of the affected limb has been revealed from CRPS patients and laboratory animals. More recently, autoimmune contributions have been implicated by the presence of pain-promoting IgG and IgM antibodies in CRPS patients and animal models (Clark et al. 2018). Notably, CRPS can be characterized as CRPS-I and CRPS-II, with the latter involving neuropathic pain.

Erythromelalgia, or Mitchell's disease (named after Silas Weir Mitchell), is a rare vascular peripheral pain disorder in which blood vessels, usually in the lower extremities or hands, are episodically blocked (frequently on and off daily), then become hyperemic and inflamed (Waxman and Dib-Hajj 2005). Patients with erythromelalgia suffer from severe burning pain and display skin redness. Pain attacks are periodic and triggered by heat, pressure, mild activity, exertion, insomnia, or stress. Erythromelalgia may result from a primary or secondary disorder. Secondary erythromelalgia can be caused by small fiber neuropathy of any cause, polycythemia vera, essential thrombocytosis, hypercholesterolemia, mushroom or mercury poisoning, and some autoimmune disorders. A major progress in human genetics of pain has revealed that primary erythromelalgia is caused by mutation of the voltage-gated sodium channel α-subunit gene *SCN9A*, encoding Nav1.7 subunit (Bennett and Woods 2014; Waxman 2013).

Finally, fibromyalgia is a chronic and widespread musculoskeletal pain condition and has been shown to demonstrate fiber neuropathy with chronic neuroinflammation (Ji et al. 2018; Sommer et al. 2018). The degree to which the acute and chronic pain is mediated by the neuroinflammatory response is still an area for investigation. Also, associated with fibromyalgia is the decreased activity of enzymes that metabolize catecholamines, such as epinephrine and norepinephrine. Subsequently, pain conditions are exacerbated and maintained for a longer period of time, which may be associated with observed increased levels of pro-inflammatory cytokines in patients with chronic pain conditions. It was found that reduction in skin innervation is associated with a severe fibromyalgia phenotype (Evdokimov et al. 2019). Unbiased immune profiling has revealed a natural killer (NK) cell–peripheral nerve axis in fibromyalgia patients. NK cells may contribute to the loss of skin nerve innervation in these patients (Verma et al. 2022). A recent study from Sweden has demonstrated that transfer of serum/autoantibodies from fibromyalgia patients to naïve mice is sufficient to induce fibromyalgia-like pain and neuroinflammation (Goebel et al. 2021).

2.9.2 Multiple Sclerosis

Multiple sclerosis is characterized by the debilitating loss of myelin. Though the pathogenesis of multiple sclerosis remains poorly understood, studies suggest that T-cell-mediated inflammation directed against myelin may contribute to the condition. Pain from severe multiple sclerosis can be immensely disabling, often requiring patients to have a caretaker (Garg and Smith 2015). The cause of the activation of T-cells against the host is unclear but may involve infectious agents from the environment. Corticosteroids in conjunction with adrenocorticotropic hormone have immunomodulatory effects that can be acute therapeutic options. Additionally, interferon injections can limit the entry of T-cells into the CNS, stabilizing the blood-brain barrier, but may cause side effects including flu-like symptoms, fluctuations in liver enzyme levels, and injection site reactions, among others (Berkovich et al. 2017; Tan et al. 2021).

2.9.3 Neuromyelitis Optica Spectrum Disorder (NMOSD)

Neuromyelitis optica spectrum disorder (NMOSD) is a disease that affects the central nervous system. In NMOSD, inflammation characteristically appears in stretches of the spinal cord and/or in the optic nerve. Patients with NMOSD often become blind and paralyzed with the progression of the disease. Although the precise cause of NMOSD is unclear, patients with NMOSD are noted to have antibodies against aquaporin-4, a channel for water in astrocytes. NMOSD is a debilitating painful disease for approximately 80% of patients, resulting in significant reduction in quality of life (Bradl et al. 2014). Antibodies against AQP4 lead to interleukin-6 (IL-6) production, resulting in decreased blood-brain-barrier functions. Additionally, astrocytes expressing AQP4 become debilitated and support for nearby oligodendrocytes and neurons become limited, leading to granulocyte infiltration and demyelination as a result of damaged oligodendrocytes. Acute treatment primarily involves high-dose steroids while long-term treatment uses immunosuppressants including anti-IL-6 treatment (Bradl et al. 2014; Ji et al. 2019).

2.9.4 Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a common form of inflammatory arthritis. Although the mechanisms of pain are not fully understood, research indicates that TNF-α and interleukin-1 cytokines are present in affected synovial fluid and tissues at higher levels. Accordingly, anti-TNF-α interventions have emerged as a treatment option to target aggravated inflammatory pathways. Severe inflammation of the diarthrodial joint is seen in rheumatoid arthritis, resulting in significantly decreased mobility

and ongoing pain. Rheumatoid arthritis is a major health issue in the USA, where it afflicts 1.3 million adults. In addition to producing major costs in terms of productivity and treatment costs, the condition significantly reduces quality of life, making it difficult for patients to perform many day-to-day tasks (Lee and Weinblatt 2001). Immunotherapies such as monoclonal antibodies against cytokines and cytokine receptors have been approved to treat RA symptoms (Kalpachidou et al. 2022). Majority of RA patients complain about pain such as joint stiffness. The effects of the immunotherapies on RA pain remain to be validated.

2.9.5 Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is a chronic autoimmune disorder. Research has demonstrated that microparticles (MPs), small membrane-bound vesicles, can contribute to the pathogenesis of SLE. In MPs, DNA and RNA may initiate and sustain autoantibody production. Additionally, the particles can source extracellular nuclear molecules to form pathogenic immune complexes, leading to elevated inflammatory responses through multiple receptor systems. Inflammation in lupus can also be visible in red, swollen joints. SLE is also a risk factor for atherosclerosis, a disease marked by fatty plaques in arteries, in adolescents, increasing the risk of myocardial infarction. Consequently, dyslipidemia patterns in pediatric SLE should be monitored routinely. In SLE, the body produces antibodies against its own antigen in cell nuclei and cytoplasm, causing damage in numerous organs. SLE can cause significant pain, usually widespread muscle stiffness or aches. Although treatable, the pain is recurrent and requires continuous treatment (Pisetsky et al. 2021).

2.10 Concluding Remarks

As a cardinal feature of inflammation, pain is naturally associated with inflammation. During inflammation, pro-inflammatory mediators are produced that can evoke pain. Thus, anti-inflammatory treatments can effectively alleviate acute pain. Acute inflammation is also beneficial for wound healing, and inflammation-produced pro-resolving mediators such as SPMs are potent inhibitors of pain. However, chronic inflammation, including neuroinflammation, can lead to various pathological conditions associated with chronic pain. It is generally believed that chronic pain persists after the observable signs and symptoms of inflammation have resolved. However, recent advances in understanding of neuroinflammation are changing this perspective. We have begun to appreciate that neuroinflammation is associated with and perhaps mediates the transition from acute to chronic pain, as well as chronification of human pain conditions. Thanks to the proximity to pain neurocircuit in the PNS and CNS, neuroinflammation-associated mediators or neuromodulators (e.g., cytokines and chemokines) are highly effective in modulating pain sensitivity.

Importantly, neuroinflammation contributes to the pathophysiology of chronic overlapping pain conditions, including but not limited to fibromyalgia, headache, temporomandibular disorder, back pain, irritable bowel syndrome, primary headaches, pelvic pain, and vestibulodynia (Ji et al. 2018). Thus, control of neuroinflammation may help to alleviate chronic overlapping pain conditions.

References

Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell. 2006;124(4):783–801.

An J, Minie M, Sasaki T, Woodward JJ, Elkon KB. Antimalarial drugs as immune modulators: new mechanisms for old drugs. Annu Rev Med. 2017;68:317–30.

Bang S, Xie YK, Zhang ZJ, Wang Z, Xu ZZ, Ji RR. Gpr37 regulates macrophage phagocytosis and resolution of inflammatory pain. J Clin Invest. 2018;128(8):3568–82.

Bang S, Donnelly CR, Luo X, Toro-Moreno M, Tao X, Wang Z, Chandra S, Bortsov AV, Derbyshire ER, Ji RR. Activation of gpr37 in macrophages confers protection against infection-induced sepsis and pain-like behaviour in mice. Nat Commun. 2021;12(1):1704.

Baral P, Udit S, Chiu IM. Pain and immunity: implications for host defence. Nat Rev Immunol. 2019;19(7):433–47.

Bennett DL, Woods CG. Painful and painless channelopathies. Lancet Neurol. 2014;13(6):587–99.

Berkovich R, Bakshi R, Amezcua L, Axtell RC, Cen SY, Tauhid S, Neema M, Steinman L. Adrenocorticotropic hormone *versus* methylprednisolone added to interferon β in patients with multiple sclerosis experiencing breakthrough disease: a randomized, rater-blinded trial. Ther Adv Neurol Disord. 2017;10(1):3–17.

Blasco B, Leroy D, Fidock DA. Antimalarial drug resistance: linking plasmodium falciparum parasite biology to the clinic. Nat Med. 2017;23(8):917–28.

Boller T, Felix G. A renaissance of elicitors: perception of microbe-associated molecular patterns and danger signals by pattern-recognition receptors. Annu Rev Plant Biol. 2009;60:379–406.

Bradl M, Kanamori Y, Nakashima I, Misu T, Fujihara K, Lassmann H, Sandkühler J. Pain in neuromyelitis optica – prevalence, pathogenesis and therapy. Nat Rev Neurol. 2014;10(9):529–36.

Brigham NC, Ji RR, Becker ML. Degradable polymeric vehicles for postoperative pain management. Nat Commun. 2021;12(1):1367.

Calvo M, Dawes JM, Bennett DL. The role of the immune system in the generation of neuropathic pain. Lancet Neurol. 2012;11(7):629–42.

Cao R, Hu H, Li Y, Wang X, Xu M, Liu J, Zhang H, Yan Y, Zhao L, Li W, et al. Anti-sars-cov-2 potential of artemisinins in vitro. ACS Infect Dis. 2020;6(9):2524–31.

Chen G, Kim YH, Li H, Luo H, Liu DL, Zhang ZJ, Lay M, Chang W, Zhang YQ, Ji RR. Pd-l1 inhibits acute and chronic pain by suppressing nociceptive neuron activity via pd-1. Nat Neurosci. 2017a;20(7):917–26.

Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X, Zhao L. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017b;9(6):7204–18.

Chen G, Zhang YQ, Qadri YJ, Serhan CN, Ji RR. Microglia in pain: detrimental and protective roles in pathogenesis and resolution of pain. Neuron. 2018;100(6):1292–311.

Chen O, Donnelly CR, Ji RR. Regulation of pain by neuro-immune interactions between macrophages and nociceptor sensory neurons. Curr Opin Neurobiol. 2020;62:17–25.

Chiu IM. Infection, pain, and itch. Neurosci Bull. 2018;34(1):109–19.

Chiu IM, von Hehn CA, Woolf CJ. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. Nat Neurosci. 2012;15(8):1063–7.

Chiu IM, Heesters BA, Ghasemlou N, von Hehn CA, Zhao F, Tran J, Wainger B, Strominger A, Muralidharan S, Horswill AR, et al. Bacteria activate sensory neurons that modulate pain and inflammation. Nature. 2013;501(7465):52–7.

Christian-Miller N, Frenette C. Hepatocellular cancer pain: impact and management challenges. J Hepatocell Carcinoma. 2018;5:75–80.

Christianson CA, Dumlao DS, Stokes JA, Dennis EA, Svensson CI, Corr M, Yaksh TL. Spinal tlr4 mediates the transition to a persistent mechanical hypersensitivity after the resolution of inflammation in serum-transferred arthritis. Pain. 2011;152(12):2881–91.

Clark DJ, Tawfik VL, Tajerian M, Kingery WS. Autoinflammatory and autoimmune contributions to complex regional pain syndrome. Mol Pain. 2018;14:1744806918799127.

Cohen JA, Edwards TN, Liu AW, Hirai T, Jones MR, Wu J, Li Y, Zhang S, Ho J, Davis BM, et al. Cutaneous TRPV1(+) neurons trigger protective innate type 17 anticipatory immunity. Cell. 2019;178(4):919–32 e914.

Corder G, Castro DC, Bruchas MR, Scherrer G. Endogenous and exogenous opioids in Pain. Annu Rev Neurosci. 2018;41:453–73.

Diogenes A, Ferraz CC, Akopian AN, Henry MA, Hargreaves KM. LPS sensitizes TRPV1 via activation of TLR4 in trigeminal sensory neurons. J Dent Res. 2011;90(6):759–64.

Donnelly CR, Chen O, Ji RR. How do sensory neurons sense danger signals? Trends Neurosci. 2020;43(10):822–38.

Erny D, Hrabe de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, Keren-Shaul H, Mahlakoiv T, Jakobshagen K, Buch T, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci. 2015;18(7):965–77.

Evdokimov D, Frank J, Klitsch A, Unterecker S, Warrings B, Serra J, Papagianni A, Saffer N, Meyer Zu Altenschildesche C, Kampik D, Malik RA, Sommer C, Üçeyler N. Reduction of skin innervation is associated with a severe fibromyalgia phenotype. Ann Neurol. 2019 Oct;86(4):504–16.

Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain Behav. 2015;5(9):e00362.

Gendrot M, Duflot I, Boxberger M, Delandre O, Jardot P, Le Bideau M, Andreani J, Fonta I, Mosnier J, Rolland C, et al. Antimalarial artemisinin-based combination therapies (act) and covid-19 in Africa: In vitro inhibition of sars-cov-2 replication by mefloquine-artesunate. Int J Infect Dis. 2020;99:437–40.

Gereau RW, Sluka KA, Maixner W, Savage SR, Price TJ, Murinson BB, Sullivan MD, Fillingim RB. A pain research agenda for the 21st century. J Pain. 2014;15(12):1203–14.

Goebel A, Krock E, Gentry C, Israel MR, Jurczak A, Urbina CM, Sandor K, Vastani N, Maurer M, Cuhadar U, Sensi S, Nomura Y, Menezes J, Baharpoor A, Brieskorn L, Sandström A, Tour J, Kadetoff D, Haglund L, Kosek E, Bevan S, Svensson CI, Andersson DA. Passive transfer of fibromyalgia symptoms from patients to mice. J Clin Invest. 2021;131(13):e144201.

Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. Nat Med. 2010;16(11):1248–57.

Gosselin RD, Suter MR, Ji RR, Decosterd I. Glial cells and chronic pain. Neuroscientist. 2010;16(5):519–31.

Guo R, Chen LH, Xing C, Liu T. Pain regulation by gut microbiota: molecular mechanisms and therapeutic potential. Br J Anaesth. 2019;123(5):637–54.

Hanani M, Spray DC. Emerging importance of satellite glia in nervous system function and dysfunction. Nat Rev Neurosci. 2020;21(9):485–98.

Heidland A, Klassen A, Rutkowski P, Bahner U. The contribution of Rudolf Virchow to the concept of inflammation: what is still of importance? J Nephrol. 2006;10(Suppl):S102–9.

Ji RR, Xu ZZ, Strichartz G, Serhan CN. Emerging roles of resolvins in the resolution of inflammation and pain. Trends Neurosci. 2011;34(11):599–609.

Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. Nat Rev Drug Discov. 2014;13(7):533–48.

Ji RR, Chamessian A, Zhang YQ. Pain regulation by non-neuronal cells and inflammation. Science. 2016;354(6312):572–7.
Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology. 2018;129(2):343–66.
Ji RR, Donnelly CR, Nedergaard M (2019) Astrocytes in chronic pain and itch. Nat Rev Neurosci. 2019;20(11):667–685. https://doi.org/10.1038/s41583-019-0218-1
Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature. 2001;413(6852):203–10.
Kalpachidou T, Riehl L, Schöpf CL, Ucar B, Kress M. Proinflammatory cytokines and their receptors as druggable targets to alleviate pathological pain. Pain. 2022;163(Suppl 1):S79–98.
Kapepula PM, Kabengele JK, Kingombe M, Van Bambeke F, Tulkens PM, Sadiki Kishabongo A, Decloedt E, Zumla A, Tiberi S, Suleman F, Tshilolo L, Muyembe-TamFum JJ, Zumla A, Nachega JB. *Artemisia* Spp. derivatives for COVID-19 treatment: anecdotal use, political hype, treatment potential, challenges, and road map to randomized clinical trials. Am J Trop Med Hyg. 2020;103(3):960–4.
Khoury DS, Cromer D, Elliott T, Soon MSF, Thomas BS, James KR, Best SE, Aogo RA, Engel JA, Gartlan KH, et al. Characterising the effect of antimalarial drugs on the maturation and clearance of murine blood-stage plasmodium parasites in vivo. Int J Parasitol. 2017;47(14):913–22.
Kvietys PR, Granger DN. Endothelial cell monolayers as a tool for studying microvascular pathophysiology. Am J Phys. 1997;273(6):G1189–99.
Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001;358(9285):903–11.
Lee DSW, Rojas OL, Gommerman JL. B cell depletion therapies in autoimmune disease: advances and mechanistic insights. Nat Rev Drug Discov. 2021;20(3):179–99.
Lei V, Handfield C, Kwock JT, Kirchner SJ, Lee MJ, Coates M, Wang K, Han Q, Wang Z, Powers JG, Wolfe S, Corcoran DL, Fanelli B, Dadlani M, Ji RR, Zhang JY, MacLeod AS. Skin injury activates a rapid TRPV1-dependent antiviral protein response. J Invest Dermatol. 2022;142(8):2249–59.e9.
Lewis WD, Lilly S, Jones KL. Lymphoma: diagnosis and treatment. Am Fam Physician. 2020;101(1):34–41.
Li WW, Guo TZ, Liang D, Shi X, Wei T, Kingery WS, Clark JD. The nalp1 inflammasome controls cytokine production and nociception in a rat fracture model of complex regional pain syndrome. Pain. 2009;147(1–3):277–86.
Liu T, Xu ZZ, Park CK, Berta T, Ji RR. Toll-like receptor 7 mediates pruritus. Nat Neurosci. 2010;13(12):1460–2.
Liu T, Gao YJ, Ji RR. Emerging role of toll-like receptors in the control of pain and itch. Neurosci Bull. 2012;28(2):131–44.
Liu XJ, Zhang Y, Liu T, Xu ZZ, Park CK, Berta T, Jiang D, Ji RR. Nociceptive neurons regulate innate and adaptive immunity and neuropathic pain through MyD88 adapter. Cell Res. 2014;24(11):1374–7.
Mainwaring T. An account of an uncommon inflammation of the epiglottis: Communicated in a Letter to Everard Home, Esq. F.R.S., and by Him to Dr. Simmons. Med Facts Obs. 1791;1:40–42. PMID: 29106131; PMCID: PMC5072801.
Marion E, Song OR, Christophe T, Babonneau J, Fenistein D, Eyer J, Letournel F, Henrion D, Clere N, Paille V, et al. Mycobacterial toxin induces analgesia in buruli ulcer by targeting the angiotensin pathways. Cell. 2014;157(7):1565–76.
Martinez Quintero B, Yazbeck C, Sweeney LB. Thyroiditis: evaluation and treatment. Am Fam Physician. 2021;104(6):609–17.
Matsuda M, Huh Y, Ji RR. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. J Anesth. 2019;33(1):131–9.
Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454(7203):428–35.
Medzhitov R. Inflammation 2010: new adventures of an old flame. Cell. 2010;140(6):771–6.
Medzhitov R. The spectrum of inflammatory responses. Science. 2021;374(6571):1070–5.

Miranda AS, Brant F, Rocha NP, Cisalpino D, Rodrigues DH, Souza DG, Machado FS, Rachid MA, Teixeira AL Jr, Campos AC. Further evidence for an anti-inflammatory role of artesunate in experimental cerebral malaria. Malar J. 2013;12:388.

Niehaus JK, Taylor-Blake B, Loo L, Simon JM, Zylka MJ. Spinal macrophages resolve nociceptive hypersensitivity after peripheral injury. Neuron. 2021;109(8):1274–82 e1276.

Park JY. Artemisinin and the Nobel Prize in physiology or medicine 2015. Korean J Pain. 2019;32(3):145–6.

Pisetsky DS, Eudy AM, Clowse MEB, Rogers JL. The categorization of pain in systemic lupus erythematosus. Rheum Dis Clin N Am. 2021;47(2):215–28.

Plytycz B, Seljelid B. From inflammation to sickness: historical perspective. Arch Immunol Ther Exp. 2003;51(2):105–9.

Riol-Blanco L, Ordovas-Montanes J, Perro M, Naval E, Thiriot A, Alvarez D, Wood JN, von Andrian UH. Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. Nature. 2014;510(7503):157–61.

Rochae e Silva M. A brief history of inflammation. In: Vane JR, Ferreira SH, editors. Inflammation. Handbook of experimental pharmacology (continuation of Handbuch der experimentellen Pharmakologie), vol. 50/1. Berlin/Heidelberg: Springer; 1978. https://doi.org/10.1007/978-3-642-66888-3_2.

Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the global burden of disease study. Lancet. 2020;395(10219):200–11.

Scrivo R, Vasile M, Bartosiewicz I, Valesini G. Inflammation as "common soil" of the multifactorial diseases. Autoimmun Rev. 2011;10(7):369–74.

Serhan CN. Resolution phase of inflammation: novel endogenous anti-inflammatory and proresolving lipid mediators and pathways. Annu Rev Immunol. 2007;25:101–37.

Shen S, Lim G, You Z, Ding W, Huang P, Ran C, Doheny J, Caravan P, Tate S, Hu K, et al. Gut microbiota is critical for the induction of chemotherapy-induced pain. Nat Neurosci. 2017;20(9):1213–6.

Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020 Apr;20(4):425–34.

Shiers S, Ray PR, Wangzhou A, Sankaranarayanan I, Tatsui CE, Rhines LD, Li Y, Uhelski ML, Dougherty PM, Price TJ. ACE2 and SCARF expression in human dorsal root ganglion nociceptors: implications for SARS-CoV-2 virus neurological effects. Pain. 2020;161(11):2494–501.

Skube ME, Beilman GJ. Surgical treatment of pain in chronic pancreatitis. Curr Opin Gastroenterol. 2018 Sep;34(5):317–21.

Sommer C, Leinders M, Üçeyler N. Inflammation in the pathophysiology of neuropathic pain. Pain. 2018;159(3):595–602.

Talbot S, Foster SL, Woolf CJ. Neuroimmunity: physiology and pathology. Annu Rev Immunol. 2016;34:421–47.

Tan PH, Ji J, Yeh CC, Ji RR. Interferons in pain and infections: emerging roles in neuro-immune and neuro-glial interactions. Front Immunol. 2021 Nov 5;12:783725. https://doi.org/10.3389/fimmu.2021.783725. eCollection 2021

Verma V, Drury GL, Parisien M, Özdağ Acarli AN, Al-Aubodah TA, Nijnik A, Wen X, Tugarinov N, Verner M, Klares R 3rd, Linton A, Krock E, Morado Urbina CE, Winsvold B, Fritsche LG, Fors EA, Piccirillo C, Khoutorsky A, Svensson CI, Fitzcharles MA, Ingelmo PM, Bernard NF, Dupuy FP, Üçeyler N, Sommer C, King IL, Meloto CB, Diatchenko L, HUNT-All In Pain. Unbiased immune profiling reveals a natural killer cell-peripheral nerve axis in fibromyalgia. Pain. 2022 July 1;163(7):e821–36. https://doi.org/10.1097/j.pain.0000000000002498.

Volkow ND, Collins FS. The role of science in addressing the opioid crisis. N Engl J Med. 2017;377(4):391–4.

Wang J, Xu C, Liao FL, Jiang T, Krishna S, Tu Y. A temporizing solution to "artemisinin resistance". N Engl J Med. 2019;380(22):2087–9.

Waxman SG. Painful Na-channelopathies: An expanding universe. Trends Mol Med. 2013;19(7):406–9.

Waxman SG, Dib-Hajj SD. Erythromelalgia: a hereditary pain syndrome enters the molecular era. Ann Neurol. 2005;57(6):785–8.

Wei T, Guo TZ, Li WW, Kingery WS, Clark JD. Acute versus chronic phase mechanisms in a rat model of CRPS. J Neuroinflammation. 2016;13:14.

Woolf CJ, Ma Q. Nociceptors – noxious stimulus detectors. Neuron. 2007;55(3):353–64.

Xanthos DN, Sandkuhler J. Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. Nat Rev Neurosci. 2014;15(1):43–53.

Xu H, He Y, Yang X, Liang L, Zhan Z, Ye Y, Yang X, Lian F, Sun L. Anti-malarial agent artesunate inhibits TNF-alpha-induced production of proinflammatory cytokines via inhibition of NF-kappaB and pi3 kinase/Akt signal pathway in human rheumatoid arthritis fibroblast-like synoviocytes. Rheumatology (Oxford). 2007;46(6):920–6.

Yang Z, Ding J, Yang C, Gao Y, Li X, Chen X, Peng Y, Fang J, Xiao S. Immunomodulatory and anti-inflammatory properties of artesunate in experimental colitis. Curr Med Chem. 2012;19(26):4541–51.

Yang NJ, Isensee J, Neel DV, Quadros AU, Zhang HB, Lauzadis J, Liu SM, Shiers S, Belu A, Palan S, et al. Anthrax toxins regulate pain signaling and can deliver molecular cargoes into ANTXR2(+) DRG sensory neurons. Nat Neurosci. 2021;25(2):168–79.

Zhang X, He Y. The role of nociceptive neurons in the pathogenesis of psoriasis. Front Immunol. 2020;11:1984.