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COMMENTARY

COVID-19 and cancer: start the resolution!

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Abstract

Coronavirus disease 2019 (COVID-19) due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been an ongoing pandemic causing significant morbidity and mortality worldwide. The "cytokine storm" is a critical driving force in severe COVID-19 cases, leading to hyperinflammation, multi-system organ failure, and death. A paradigm shift is emerging in our understanding of the resolution of inflammation from a passive course to an active biochemical process driven by endogenous specialized pro-resolving mediators (SPMs), such as resolvins, protectins, lipoxins, and maresins. SPMs stimulate macrophage-mediated debris clearance and counter pro-inflammatory cytokine production, a process collectively termed as the "resolution of inflammation." Hyperinflammation is not unique to COVID-19 and also occurs in neoplastic conditions, putting individuals with underlying health conditions such as cancer at elevated risk of severe SARS-CoV-2 infection. Despite approaches to block systemic inflammation, there are no current therapies designed to stimulate the resolution of inflammation in patients with COVID-19 or cancer. A non-immunosuppressive therapeutic approach that reduces the cytokine storm in patients with COVID-19 and cancer is urgently needed. SPMs are potent immunoresolvent and organ-protective lipid autacoids that stimulate the resolution of inflammation, facilitate clearance of infections, reduce thrombus burden, and promote a return to tissue homeostasis. Targeting endogenous lipid mediators, such as SPMs, offers an entirely novel approach to control SARS-CoV-2 infection and cancer by increasing the body's natural reserve of pro-resolving mediators without overt toxicity or immunosuppression.

Keywords COVID-19 · Cytokine storm · SARS-CoV-2 · Resolution of inflammation

1 Introduction

Multiple human diseases, including coronavirus disease 2019 (COVID-19) and cancer, are driven by unresolved inflammation [1, 2]. Self-limited, acute inflammation, when properly regulated, is a natural host response to injury or invading pathogens that helps restore homeostasis. This coordinated and host-protective process is initiated by the recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) by host cells. PAMPs are common motifs found within classes of microbes, e.g., severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, while DAMPs are molecules released following tissue injury from dying or damaged cells, e.g. cancer. PAMPs and DAMPs are both detected by pattern recognition receptors (PRRs), which include Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)–like receptors, nucleotide-binding

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oligomerization domain (NOD)–like receptors, and C-type lectin receptors, expressed in innate and adaptive immune cells [3, 4]. Upon PRR activation, signal transduction pathways lead to the activation of transcription factors, including nuclear factor-κB (NF-κB), activator protein 1 (AP-1), interferon-regulated genes (IRGs), and CCAAT enhancer-binding protein beta (C/EBPβ), which upregulate gene expression and the synthesis of pro-inflammatory mediators that coordinate the elimination of pathogens and infected or damaged cells. Inflammatory enzymes locally produce arachidonic acid–derived eicosanoids, such as prostaglandins (PG), leukotrienes (LT), and thromboxanes (TX), which mediate the generation of cytokines and chemokines contributing to a "cytokine storm." Together, these eicosanoids and their downstream mediators contribute to the classical symptoms of inflammation [2, 5–8] first documented by Roman doctor Cornelius Celsus in the first century AD, which include redness (rubor), heat (calor), swelling (tumor), and pain (dolor), and later the addition of loss of function (function laesa) by Rudolph Virchow in the nineteenth century AD [9].

Phagocytosis of microbial invaders and cellular debris by macrophages should control and self-limit the acute inflammatory process, thereby allowing the damaged tissue to begin regeneration and return to homeostasis [10]. However, if there is unsuccessful removal of noxious stimuli, macrophages continue to act as antigen-presenting cells for T cells, turning acute and physiological inflammation into chronic and pathological [11]. Without adequate clearance, inflammasomes can become activated, triggering a macrophage-derived "eicosanoid storm" of endogenously produced lipid mediators that leads to a cytokine storm with the release of pro-inflammatory cytokines and chemokines, inducing a persistent hyperinflammatory state (Fig. 1) [12]. Hence, sustained pathologic inflammation can cause excessive tissue damage and exacerbate the disease state beyond the acute inflammatory response associated with the initial infection or disease itself. This scenario has been observed

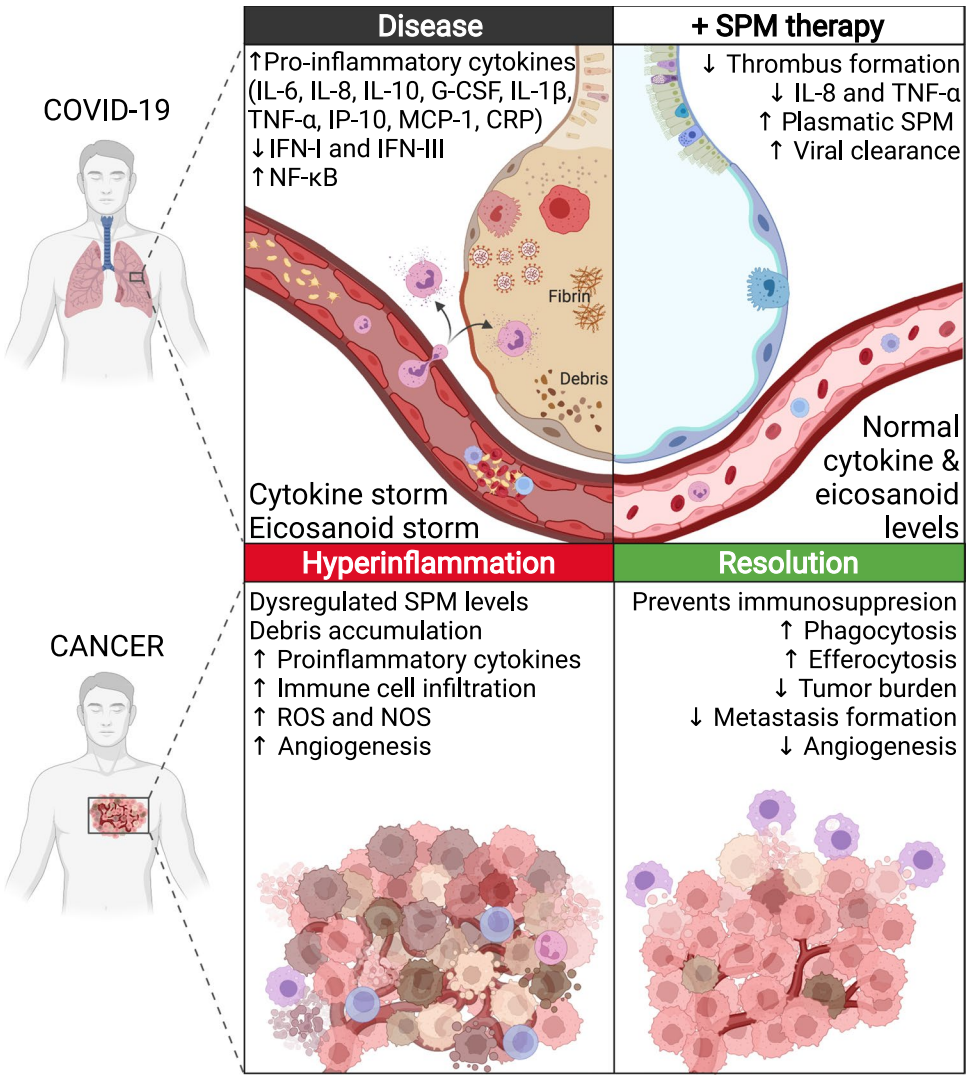

Fig. 1 Hyperinflammation in COVID-19 and cancer occurs due to a cascade of events, including the activation of transcription factors, the production of inflammatory enzymes, and the release of eicosanoids and pro-inflammatory cytokines. These mediators enhance ongoing inflammation, contributing to disease progression and tissue destruction. SPMs, including resolvins, protectins, lipoxins, and maresins, exert their pro-resolving and anti-inflammatory effects by stimulating clearance of noxious stimuli (phagocytosis of SARS-CoV-2 and phagocytosis/efferocytosis of cancer debris), countering the "cytokine storm," and exhibiting anti-thrombotic properties. Created with BioRender.com

in cancer and COVID-19, both of which have caused widespread morbidity and mortality. Early observations have identified an association between a hyperinflammatory cytokine storm and poor clinical outcomes among patients with COVID-19 [1, 13, 14]. Thus, the pro-inflammatory cytokine storm likely represents a critical driving force in severe COVID-19, potentially leading to sequela such as a systemic inflammatory response and multi-system organ failure in those infected with SARS-CoV-2 [1, 15, 16].

Historically, the resolution of inflammation was considered a passive process, resulting from the loss or dilution of pro-inflammatory mediators from the extracellular milieu [17]. Thus, anti-inflammatory therapies have focused on neutralizing pro-inflammatory mediators, including cytokines, eicosanoids, and their biosynthetic enzymes [18–20]. Despite approaches to block systemic inflammation, there are no current therapies designed to stimulate the resolution of inflammation in patients with COVID-19 or cancer. Although previously believed to be passive, resolution of inflammation is now known to be an active biochemical process orchestrated by lipid autacoids known as specialized pro-resolving mediators (SPMs). SPMs, which include the lipoxin (LX), resolvin (Rv), protectin (PD), and maresin (MaR) families, are biosynthesized from polyunsaturated fatty acids, including arachidonic acid, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and n-3 docosapentaenoic acid [21–23]. Through stereoselective activation of their specific G-protein-coupled receptors (GPCRs), SPMs evoke anti-inflammatory and pro-resolving processes without being immunosuppressive [2, 24]. Professor CN Serhan outlined the basics of the resolution response and mechanisms as well as the potential impact of resolution mediators in tissue regeneration in recent talks to the National Institute of Health (NIH) (https://www.niams.nih.gov/newsroom/featured/inflammation-resolution-roundtable) and to the National Academies of Sciences, Engineering, and Medicine (https://www.nationalacademies.org/event/11-02-2021/understanding-the-role-of-the-immune-system-in-improving-tissue-regeneration-a-workshop). Notably, while some drugs can disrupt timely resolution, aspirin and statins trigger the production of epimeric forms of several SPMs, further promoting the resolution of inflammation [22, 25–30].

Failure to resolve inflammation has been linked to pathologic inflammation in several diseases due to impaired biosynthesis of SPMs, including tuberculous meningitis, multiple sclerosis, and osteoarthritis [31–33]. In fact, within various hyperinflammatory diseases, eicosanoids, SPMs, and SPM/eicosanoid ratios in peripheral blood have been identified as novel serological biomarkers to monitor disease and treatment efficacy [34]. Dysregulated levels of SPMs with elevated eicosanoid patterns (e.g., reduced SPM/eicosanoid ratio such as resolvin D1/leukotriene B_4) have been detected in human patients with various inflammatory diseases, including sepsis, chronic obstructive pulmonary disease (COPD), colon cancer, and leukemia [34]. Possible explanations for reduced SPM levels include reduced dietary intake of EPA and DHA as well as mutations in enzymes involved in synthesizing SPMs. Other mechanisms that may also disrupt inflammation resolution include mutations in the genes encoding SPM receptors, diminished expression of SPM receptors, dysfunctional SPM receptors, and abnormal post-SPM receptor intracellular signaling [35, 36]. Failure of resolution, sometimes termed a "resolution deficit," can thus contribute to hyperinflammation in COVID-19 and cancer via uncontrolled eicosanoid and cytokine storms [13, 37, 38]. The direct activity of released cytokines and chemokines in COVID-19 and cancer can cause massive cell death that provokes an ongoing cascade of host responses, including the production of macrophage-derived eicosanoids, that potentiates a vicious cycle of eicosanoid and cytokine storms [2, 39, 40]. Although endogenously produced SPMs exhibit potent inflammation-resolving activities by controlling leukocyte trafficking and countering the production of cytokines and chemokines, absent or diminished SPM levels may allow for ongoing pro-inflammatory processes [2]. Here, building off of a previous review [16], we elucidate parallels between COVID-19 and cancer, highlighting how impaired endogenous pro-resolving pathways may contribute to the hyperinflammation seen in both disease pathologies and offering insight into possible therapeutic interventions moving forward.

2 Inflammation in COVID-19

A well-coordinated immune response is critical for defense against viral infections. Hence, dysregulation of the host response can lead to severe tissue damage, exacerbated microbial burden, and progressive disease pathology. The sequela of the inflammatory response that results from SARS-CoV-2 infection can have lasting health complications on patients of all ages, leading to multi-system inflammatory syndrome in children (MIS-C) [41] as well as acute respiratory distress syndrome (ARDS) and multi-system organ failure in adults [42]. The resulting impact on human life has been significant with over five million deaths attributed to COVID-19 globally as of December 2021 [43].

Increased levels of many cytokines and chemokines have previously been demonstrated in humans infected with SARS-associated coronavirus [44–47]. Elevated interleukin 6 (IL-6), IL-10, IL-2 receptor, and tumor necrosis factor alpha (TNF-α) levels were recently reported in COVID-19 patients and found to correlate with disease severity [48]. Notably, higher plasma levels of IL-2, IL-6, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), interferon

gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage-inflammatory protein 1α (MIP-1α/CCL3), and TNF-α were identified in patients with confirmed SARS-CoV-2 infection requiring intensive care [13, 49]. In one retrospective multi-center study involving 150 hospitalized patients from Wuhan, China, significant differences were identified in plasma levels of inflammatory markers, including IL-6 and C-reactive protein (CRP), between patients who died of COVID-19 versus those discharged [50]. Additionally, increased expression of C–C motif chemokine receptor 5 (CCR5) has been identified in leukocytes of COVID-19 patients compared to healthy controls [51]. These differences suggest that pro-inflammatory mediators can serve as prognostic indicators and should be considered when developing new therapeutic approaches for treating disease complications associated with SARS-CoV-2 infection [50].

Preclinical studies have characterized the inflammatory response resulting from infection with SARS-CoV-2. In animal studies, SARS-CoV-2 has been shown to elicit a strong pro-inflammatory cytokine response after viral infection, culminating in a cytokine storm and reduced pulmonary function associated with lung infiltration by monocytes, neutrophils, and activated T cells [52]. Notably, host response to SARS-CoV-2 infection results in elevated production of chemokines and cytokines, specifically IL-6, while failing to launch a robust interferon (IFN)-I or IFN-III response [53]. Thus, hyperinflammation may result from delayed IFN-I signaling in the presence of rapid SARS-CoV-2 viral replication, allowing for accumulation of pathogenic macrophages, elevated cytokine and chemokine levels, vascular leakage, and impaired T cell responses [54]. Cynomolgus macaques with various clinical conditions and ages infected with SARS-CoV-2 also demonstrated a difference in condition severity between young and older animals with underlying diseases [55]. Despite similar viral loads, the excessive immune response seen in older animals corresponded with more severe lung injury. Of note, it has previously been shown that SARS-CoV-infected aged macaques had an exacerbated innate immune response relative to young adult macaques, which was associated with increased expression of inflammatory genes, such as NF-κB, and reduced expression of IFN-I [56]. In some patients with life-threatening COVID-19 pneumonia, genetic defects at loci involved in the induction and amplification of IFN-I as well as auto-antibodies that neutralize IFN-I were identified [57, 58]. Therapeutic approaches to COVID-19 must therefore account for the hyperinflammatory host response that results from infection with SARS-CoV-2, especially among those with loss of IFN-I-dependent immunity [59].

The SARS-CoV spike (S) protein binds to the angiotensin-converting enzyme 2 (ACE2) for viral entry into host cells [60]. The S protein has been shown to significantly induce endoplasmic reticulum (ER) stress and upregulate early expressed chemokines such as chemokine (C-X-C motif) ligand (CXCL2) in murine models (analogous to human IL-8) [61, 62]. Interestingly, coronavirus infection activates ER stress signaling and induces unfolded protein response (UPR) components at the mRNA level while suppressing them at the protein level [63]. Prolonged ER stress, with the accumulation of unfolded proteins and the consequent induction of UPR, can result in apoptotic cell death and promote an ongoing pro-inflammatory response [64]. Many groups have reported the effect of coronavirus infection on apoptosis over the last decade, and more recently, SARS-CoV-2 has also been shown to induce apoptotic cell death. Ren and collaborators have shown that SARS-CoV-2 ORF3a protein can efficiently induce apoptosis in different cell lines [65, 66]. Altogether, the delayed IFN-I response, increased ER stress, and the subsequent presence of apoptotic cellular debris lead to the development of hyperinflammation via a cytokine storm.

Signaling from cytokines and chemokines serves as an attractant for immune cells, such as neutrophils and macrophages, whose infiltration can result in tissue injury and significant detriment to organs. For example, higher levels of pro-inflammatory cytokines in the urine of patients with COVID-19 have been shown to correlate with kidney tissue damage and acute kidney injury [67]. Other organs impacted by severe COVID-19 include the lungs, heart, spleen, lymph nodes, brain, liver, eyes, vasculature, and skin [68]. In the lungs, differences between moderate and severe COVID-19 cases may result from immune cell extravasation and the presence of non-resident macrophages in the airway epithelium over-expressing cytokines and chemokines. Interestingly, single-cell sequencing analysis revealed stronger interactions between epithelial and immune cells in the airway epithelium of critically ill COVID-19 patients compared to moderate cases, indicated by the profiles of ligand-receptor expression and activated immune cells. The airway epithelium also contained inflammatory macrophages expressing high levels of C–C motif chemokine ligand 2 (CCL2), CCL3, CCL20, CXCL1, CXCL3, CXCL10, IL-8, IL-1β, and TNF-α [69]. This evidence suggests that a cytokine storm likely explains some of the pathologies associated with severe COVID-19 [1].

A broad array of inflammatory cytokines and chemokines is evident in COVID-19 pathogenesis, i.e., children suffering from MIS-C presented with elevated levels of soluble IL-2 receptor, IL-10, and IL-6 [70]. Thus, efforts to suppress hyperinflammation intrinsic to severe disease should ideally not only target specific inflammatory components but rather aim to resolve inflammation in its entirety. Of note, down-regulation of systemic SPM concentrations has been linked with dysregulated phagocyte function and increased disease severity in COVID-19 [71]. Among hospitalized critically

ill COVID-19 patients, plasma SPMs levels were found to be significantly decreased in those who died of the disease compared to those who were discharged [72]. Therefore, the link between SPM and patient survival suggests that the hyperinflammation present in severe COVID-19 may reflect failed engagement of pro-resolving pathways in inflammation resolution. Thus, rescuing failed resolution may be an ideal approach to treat COVID-19.

3 Inflammation in cancer

Inflammation is now a well-recognized hallmark of cancer [73]. While initially believed to be anti-tumoral, the impact of a tumor-associated inflammatory response on tumorigenesis, cancer progression, and metastasis is now appreciated [73, 74]. At sites of inflammation, phagocytes produce reactive oxygen and nitrogen species that can damage DNA, and chronically inflamed tissues promote cell proliferation, thus multiplying malignant cells [75]. In fact, several inflammatory states have been linked to cancer, such as inflammatory bowel disease and colorectal cancer, bronchitis and lung cancer, and prostatitis and prostate cancer [76]. The infiltration of immune cells into the tumor stroma contributes to an inflammatory milieu similar to that seen in non-neoplastic processes [77], contributing to tumor progression [78–81]. Among recruited inflammatory cells, persistent activation of transcription factors such as NF-κB, signal transducer and activator of transcription 3 (STAT3), and hypoxia-inducible factor 1α (HIF-1α) results in the production of mediators including cytokines, chemokines, and cyclooxygenase 2 (COX-2) [82]. A pathologic inflammatory cycle continues as the cytokines activate transcription factors in cells, leading to the continual production of inflammatory mediators.

Within this pro-inflammatory milieu, tumor cells can proliferate while circumventing death and invading new tissues by releasing growth factors, survival factors, and pro-angiogenic factors [39, 83–87]. Several pro-inflammatory mediators, such as TNF-α, IL-6, transforming growth factor beta (TGF-β), IL-10, CCL2, and CCL20, have been shown to attract macrophages and participate in both the initiation and progression of cancer [82, 88, 89]. Among in vitro cutaneous melanoma cells, secretion of IL-1 and TNF-α from macrophages has been shown to upregulate expression of the pro-angiogenic factors IL-8 and vascular endothelial growth factor (VEGF), thus promoting angiogenesis [90].

The cytokine storm is also critical to cancer progression and metastasis. In non-small cell lung cancer patients, elevated IL-6 and TNF-α levels in tissue and serum samples were associated with metastasis and worsened tumor clinical stage, highlighting the critical role that cytokines play in tumor cell proliferation [91]. On the other hand, IL-1β inhibitors aimed to treat inflammation in myocardial infarction patients led to reduced cancer mortality, reinforcing that pro-inflammatory IL-1β aids in the progression and invasiveness of cancers [92]. Studies involving murine models have revealed that chemokine receptors also aid in metastasis, as the expression of different receptors results in different metastatic destinations [93]. In mouse models of B16 melanoma, cells overexpressing CCR7 metastasized to lymph nodes, whereas overexpression of CXCR4 increased metastasis to the lungs [94, 95]. Metastasis, however, can be controlled through eicosanoid receptor inhibition, as PGE_2 plays a role in suppressing immune responses. In mice deficient in the PGE_2 receptor subtype 2 (EP2), lung tumor multiplicity was significantly lower than in wild-type counterparts, suggesting the PGE_2 signaling pathway as a potential therapeutic target [96].

Beyond the inflammatory nature of cancer itself, its treatment also can generate debris that further fuels a hyperinflammatory state. Although previously believed to be inert or inhibitory of tumor growth [84, 97], the cellular debris generated by current cancer therapies, including radiation and chemotherapy, can stimulate ongoing inflammation. The Revesz effect, first described in 1956, demonstrates that tumor growth can be stimulated by radiation-induced cell death via an inflammatory response [98]. In fact, co-injection of cell debris with live tumor cells reduces the inoculum of tumor cells needed to produce tumors in animal models [98–100]. Numerous studies have since confirmed that radiation-generated cellular debris drives tumorigenesis and have outlined similar effects from chemotherapy-induced cell death as well, linking this tumorigenesis to a hyperinflammatory state sustained by cytokine storms [99, 101–103]. Moreover, apoptotic cell death has been found to correlate with poor prognosis [104–108]. We recently demonstrated that cellular debris could also stimulate tumor dormancy escape via failure of resolution of inflammation and that resolvins prevent the chemotherapy-induced cytokine storm in cancer models [84]. Thus, a failure of inflammation resolution within cancer permits a sustained hyperinflammatory state, triggering cancer initiation, progression, and metastasis [85]. Given that the balance between pro- and anti-inflammatory chemokines and cytokines governs neoplastic growth [88], this highlights the critical need to supplement current treatment practices with therapeutic approaches that counter inflammation and promote its resolution.

4 Cytokine storm in COVID-19 and cancer

As outlined above, the cytokine storm is central to the pathogenesis of both COVID-19 and cancer. Additionally, both involve cell death and the generation of cellular debris that can further contribute to the cytokine storm and hyperinflammation. Analyses of the cytokine storm mediators in

cancer reveal a broad overlap with those observed in the cytokine storm in COVID-19: IL-6, MCP-1, IL-8, TNFα, G-CSF, IL-2R, IL-1β, IFN-γ, IP-10, and IL-1 [1, 13, 39, 109]. Thus, therapeutic strategies that promote resolution and work to counter a broad array of inflammatory mediators may be useful in controlling both COVID-19 and cancer.

5 Traditional approaches to counter inflammation

With both local and systemic inflammatory responses in COVID-19 and cancer, countering inflammation may be as critical as anti-SARS-CoV-2 or anti-cancer therapies themselves. Efforts to resolve inflammation date back to the ancient Greeks, who postulated that the redness in inflammation was due to an excess of red blood and practiced bloodletting as a means to reduce inflammation [110]. This theory remained in practice into the nineteenth century. Additional attempts to mitigate the pain and fever associated with inflammation were made, including Hippocrates' use of salicylates from willow bark trees in 400 BC [111]. Yet it was not until 1897 that acetyl-salicylic acid (aspirin) was patented by Bayer & Co.'s chemist Felix Hoffmann [112]. Still, aspirin's exact mechanism of action was not well elucidated until 1971, when Sir John Vane discovered that the inhibition of prostaglandin biosynthesis is the target of aspirin-like drugs [113, 114]. Within the arachidonic pathway, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the activity of COX-1 and COX-2 (except for COX-2-selective NSAIDs like celecoxib), blocking the formation of PGs that cause inflammation, swelling, pain, and fever, therefore providing antipyretic, analgesic, and anti-inflammatory relief [114]. Subsequent therapeutic approaches to suppress inflammation and immune system activation similarly center on the blockade of individual enzymes or mediators rather than attempting to dampen the entire inflammatory response [85, 115].

Many current treatments for COVID-19, including steroids, act through anti-inflammatory or immunomodulatory functions without prompting viral clearance [116]. Dexamethasone, a long-acting corticosteroid currently in use for COVID-19 patients requiring supplemental oxygen or ventilatory support, binds to glucocorticoid receptors in the cytoplasm, decreases the expression of pro-inflammatory cytokines including IL-1, IL-2, IL-6, IL-8, TNF, and IFN-γ [117], and suppresses neutrophil migration [118]. One meta-analysis encompassing data from 1,282 critically ill patients demonstrated a lower 28-day all-cause mortality in COVID-19 patients receiving systemic dexamethasone compared to placebo [119]. However, the immunosuppressive nature of glucocorticoids can leave patients vulnerable to secondary bacterial, fungal, or *Strongyloides* superinfections [120]. Selective cytokine blockade has also been employed against severe COVID-19, including the IL-6 inhibitors tocilizumab [121] and sarilumab [122]. In a fixed-effects meta-analysis that included 10,930 participants from twenty-seven randomized controlled trials, IL-6 antagonists were associated with a lower 28-day mortality among COVID-19 cases compared to placebo (summary OR 0.86, 95% CI 0.79–0.95, $p = 0.003$) [123]. Of note, a large percentage of COVID-19 patients within these trials had secondary infections by 28 days (21.9% of patients receiving IL-6 antagonists versus 17.6% of patients receiving usual care or placebo) [123]. Despite some success, these anti-inflammatory and immunomodulatory therapies leave much room for improvement as patients continue to suffer from profound morbidity due to immunosuppression and risk for secondary infections [124].

Although inflammation is fully recognized as one of the hallmarks of cancer, therapeutic approaches to counter cancer-associated inflammation have yet to be fully implemented despite robust preclinical data [125]. For example, the genetic ablation of COX or PGE synthases has been shown to shift the tumor inflammatory profile toward anti-cancer pathways. Yet therapeutic strategies targeting these mechanisms remain underutilized despite evidence that PGE_2 fuels tumor-promoting inflammation that leads to tumor growth in immunocompetent hosts [126]. While NSAIDs are starting to be clinically applied in cancer prevention, including with the US Preventive Services Task Force's recommendations on the use of aspirin to prevent colorectal cancer in adults aged 50 to 59 years, anti-inflammatory strategies are not yet included in the standard of care for anti-cancer regimens [127]. However, one analysis of five randomized controlled trials demonstrated that allocation to aspirin reduced the risk of cancer with distant metastases (hazard ratio 0.64, 95% CI 0.48–0.84, $p = 0.001$), suggesting that patients with cancer may benefit from aspirin and its anti-metastatic properties [128]. Additionally, the intraoperative administration of the NSAID ketorolac demonstrated a statistically significant reduction in the incidence of distant recurrences of breast cancer [129]. Moreover, a significant survival benefit from aspirin use has been observed for patients with esophageal, hepatobiliary, and colorectal cancers [130]. Currently, several clinical trials are underway to characterize the potential survival benefit of aspirin treatment for patients with colorectal cancer [131–134]. In addition, other approaches that target inflammation, such as the inhibition of specific cytokines and chemokines, including IL-1α (MABp1) and TNF-α (etanercept and infliximab), are showing promising results in preclinical and clinical trials [135–138]. While these findings support the addition of anti-inflammatory therapeutics to standard treatment

regimens, their success may be limited due to their targeting of specific inflammatory markers rather than system-wide inflammation.

Importantly, multiple side effects and toxicities further confound the benefits of NSAID treatment for patients with cancer. Gastrointestinal complications can be severe, including mucosal ulceration leading to peptic ulcers, reflux esophagitis, and dyspepsia. In fact, aspirin has been shown to increase upper and lower gastrointestinal bleeding risk by 60% (multivariable hazard ratio 1.62, 95% CI 1.25–2.10, $p < 0.001$) in adults aged ≥ 70 years in the ASPirin in Reducing Events in the Elderly (ASPREE) trial [139]. Furthermore, COX inhibition decreases thromboxane A2 production in platelets, which prolongs bleeding time and disrupts platelet aggregation. Additionally, the shift from the COX to the LOX pathway that occurs with NSAID use can lead to severe bronchoconstriction events in asthmatics [140]. Notably, while selective COX-2 inhibitors, such as celecoxib and rofecoxib, have been shown to prevent colorectal adenomas, their use is not routinely advised due to an increased risk of adverse cardiovascular events [141–143]. Therefore, the use of current anti-inflammatory therapies is complicated by their inability to effectively resolve inflammation as they only target specific components, and by the side effects and adverse events that occur following treatment. Approaches that address the entire pathologic process are urgently needed, especially for hyperinflammatory conditions such as COVID-19 and cancer.

6 Resolution of inflammation as a new therapeutic target

While traditional approaches to counter inflammation have focused on utilizing anti-inflammatory mechanisms, a new therapeutic direction involves harnessing the host's endogenous inflammation resolution processes, thereby eradicating the excessive inflammation rather than just dampening one component [144]. Despite some success with anti-inflammatory treatment strategies that target individual enzymes or mediators, hyperinflammatory responses seen in COVID-19, cancer, and other inflammatory diseases may require more comprehensive pharmacologic options that act not only to counter inflammation but also to promote resolution. While dexamethasone has been found to induce DHA-derived SPM production, increasing levels of protectins PD1 and PDX, its immunosuppressive properties have important implications for viral clearance and potential bacterial superinfection, as mentioned above [145, 146]. In addition to many potential adverse events, NSAIDs also indiscriminately inhibit eicosanoid pathways, thereby preventing the production of pro-resolving mediators. Blockade of COX-2 can perpetuate rather than terminate inflammation as prostaglandins play critical roles in pro-resolution processes, including initiating lipid mediator class-switching [147, 148].

Moreover, using traditional anti-inflammatory treatments is further complicated by their inability to clear debris. SPMs, on the other hand, help to orchestrate the return to tissue homeostasis through the clearance of cellular debris by regulating neutrophil infiltration and stimulating efferocytosis through the non-phlogistic recruitment of mononuclear cells [35, 149]. Since debris is critical to COVID-19 and cancer pathogenesis, it is imperative that SPMs be considered for clinical use in these pathologies. Additionally, given the cytokine storms associated with hyperinflammation in COVID-19 and cancer, it is important to note that SPMs promote inflammation resolution via downregulation of cytokine production by activated CD8 + cytotoxic T cells and CD4 + T helper (Th) 1 and Th17 cells [150]. In preclinical studies focused on cancer, resolvins counter-regulated the macrophage secretion of IL-6, IL-8, CCL4, CCL5, and TNF-α when exposed to chemotherapy-generated cellular debris [84]. Interestingly, a targeted lipidomic analysis of bronchoalveolar lavage (BAL) fluid via tandem mass spectrometry identified an increase in both pro-inflammatory lipid mediators (PGs, LTs, and TX) as well as pro-resolving lipid mediators (Rv D-series, PDX) in severe COVID-19 patients ($n = 33$) compared to healthy controls ($n = 25$) [151]. Similarly, the SARS-CoV-2 virion spike 1 glycoprotein (S1), a component of the spike protein, has been shown to increase chemokine and cytokine release, such as IL-8 and TNF-α, and trigger the biosynthesis of RvD1 in macrophages in vitro [152]. Despite this endogenous SPM production, treatment with RvD1 and RvD2 countered the S1-induced cytokine storm and hyperinflammation by significantly reducing both IL-8 and TNF-α [152], highlighting that an inflammatory milieu that is already producing resolvins may benefit from additional supplementation.

7 SPMs exhibit anti-viral and anti-thrombotic activities

SPMs, including RvE1, PD1, and PDX, have shown direct anti-viral activities [153–159]. Protectin D1 markedly attenuated influenza (H5N1) viral replication by inhibiting nuclear export of influenza virus RNA and demonstrated a survival benefit in mice with severe influenza infection [153]. Thus, PD1 effectively restricts influenza replication, even when treatment was initiated 2 days post-viral infection [153, 159]. Moreover, topical RvE1 and PD1 reduced the severity and frequency of herpes simplex virus (HSV)-1-induced inflammatory ocular lesions in murine models by enhancing microbial clearance [157, 158]. The direct and indirect anti-viral activities of SPMs in various viral diseases in humans and animal models, including the production of anti-viral antibodies and

the stimulation of lymphocytic activity, highlight their potential use in the treatment of COVID-19 [154–157, 159]. Thus, utilizing SPMs or their precursors in combination with antiviral drugs or vaccines may be a novel, effective, and practical therapeutic approach to combat COVID-19.

Critically, in addition to being anti-viral, SPMs are organ-protective and mitigate inflammation-driven lung injury. RvD1, PDX, and MaR1 injected intravenously 8 h after lipopolysaccharide-induced acute lung injury markedly stimulated alveolar fluid clearance, ultimately resulting in decreased pulmonary edema within an in vivo model [160–162]. Also, in *Escherichia coli*–induced lung injury, aspirin-triggered (AT) 15-epi-LXA_4 and 17-epi-RvD1 facilitated inflammation resolution by stimulating bacterial clearance and restoring impaired phagocytosis [163]. Lung injury leading to ARDS has dire implications for the morbidity and mortality of patients with COVID-19 [164]; hence, SPMs may represent a novel treatment option given their preclinical success in such inflammatory lung conditions.

In addition to their anti-inflammatory, pro-resolving, and anti-viral properties, SPMs have also been shown to attenuate the severity of pathological thrombosis, providing even more compelling evidence for their use in hypercoagulable conditions like cancer and COVID-19. In a cohort of 62 patients, autopsies demonstrated that patients who died of COVID-19 complications had dysregulated immunothrombosis, evidenced by the presence of neutrophil extracellular traps (NETs) associated with fibrin and platelets, which was not observed in autopsies of non-COVID-19 patients [165]. Moreover, lipid mediator metabololipidomic analysis has demonstrated that RvD1, RvD2, RvD3, RvD5, and RvE1 as well as AT-RvD3 and AT-LXB_4 were absent in patients with coronary artery disease but present in healthy individuals, suggesting that failed local resolution may lead to uncontrolled inflammation and subsequent thrombosis in these patients [166]. Notably, treatment with Lovaza, a pharmacologic preparation of the n-3 fatty acids EPA and DHA, resulted in significantly higher levels of combined AT-RvD3, RvD6, AT-PD1, and AT-LXB_4 in patients with coronary artery disease compared to those not receiving Lovaza [166]. SPMs were subsequently shown to significantly increase macrophage phagocytosis of clots by an average of approximately 50% [166]. Similarly, in a murine model of deep venous thrombosis (DVT), RvD4 significantly reduced thrombus burden and decreased the release of NETs [167].

8 The application of SPMs in COVID-19 and cancer

A non-immunosuppressive therapeutic approach is urgently needed to stimulate the resolution of inflammation and reduce the cytokine storm in patients with COVID-19 and cancer. SPMs act selectively by promoting endogenous inflammation resolution, clearing inflammatory exudates, and promoting a return to tissue homeostasis, as demonstrated in many inflammatory disease models. Therefore, SPMs are particularly well-suited for application to treat the hyperinflammation associated with cancer and COVID-19 and may also provide an additional benefit of anti-viral and anti-thrombotic activity (Fig. 1). Notably, SPMs act at significantly lower doses compared with conventional anti-inflammatory agents and are not immunosuppressive [2].

Risk factors for severe COVID-19 and cancer include comorbidities such as obesity and COPD [168], both of which have been hypothesized to confer more adverse outcomes due to SPM dysregulation or deficiencies [169–171]. Importantly, failure of inflammation resolution can be rescued in humans, as evidenced by the increase in systemic resolvin levels and upregulation of resolvin receptors in women with obesity receiving omega-3 fatty acid supplementation [172]. Similarly, parenteral fish oil emulsions and omega-3 fatty acid supplementations have been proposed to treat critically ill COVID-19 patients since the high contents of SPM precursors EPA and DHA may subsequently aid in controlling the hyperinflammatory cytokine storm [173–176]. A randomized, double-blind, placebo-controlled study showed that oral administration of enriched marine oil increases SPM levels in peripheral blood [177]. Additionally, there is a critical unmet medical need to block the cytokine storm in COVID-19 patients who also require cancer chemotherapy. Establishing new models to investigate cancer therapy-mediated effects on COVID-19 is paramount for identifying new treatment modalities to prevent the cytokine storm with severe COVID-19 in cancer patients receiving cytotoxic cancer therapies. Simultaneously blocking the pro-inflammatory response and activating endogenous resolution of inflammation programs before cancer therapy may eliminate micrometastases, reduce tumor recurrence, and mitigate the cytokine storm in this patient subset [178].

In addition to SPMs, molecules known as conjugates in tissue regeneration, including maresin conjugates in tissue regeneration (MCTR), protectin conjugates in tissue regeneration (PCTR), and resolvin conjugates in tissue regeneration (RCTR), play a key role in promoting tissue regeneration beyond inflammation resolution [179]. Recent publications have shown that PCTR1 and PD1 are upregulated during respiratory syncytial virus (RSV) pneumonia, with overlapping and distinct mechanisms for PCTR1 and PD1 during the resolution of viral infection and its associated inflammation [180]. Further research is needed to confirm the role of these novel mediators in hyperinflammatory conditions like cancer and COVID-19. Nonetheless, the direct application of SPMs is currently being studied as a therapeutic option for several diseases in humans, including COVID-19 and cancer [181–183].

Importantly, SPMs have been in clinical trials for inflammatory diseases, including infantile eczema, asthma, and dry eye disease, highlighting their safety and potential for translation to patients suffering from COVID-19 and cancer [184, 185]. As already mentioned, treatment with SPMs in cancer mouse models has resulted in significant inhibition of tumor growth [84], and the preoperative administration of the NSAID ketorolac with resolvins has been shown to synergistically eradicate the occurrence of micrometastases after primary tumor resection [178]. Currently, plans are in development to begin clinical trials to test RvE1 in solid tumor neoplasms. While the application of SPMs has yet to be further studied in COVID-19, dysregulated lipid mediator profiles in patient sera have been found to differentiate moderate from severe COVID-19 disease [186]. Thus, despite underlying etiological differences between SARS-CoV-2 infection and cancer, the similar pathologic inflammatory response suggests that promoting the resolution of inflammation through the application of SPMs, either by inducing their endogenous production and/or supplementing with exogenous administration, is an underutilized therapeutic option. Through their pro-resolving, anti-inflammatory, anti-viral, and anti-thrombotic properties, SPMs offer an entirely novel approach to control SARS-CoV-2 infection and cancer with limited side effects by increasing the body's natural reserve of pro-resolving mediators.

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