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Review Article

Chemotherapy-Induced Mucositis: A Comprehensive Review of ROS, Inflammasome Activation, and Therapeutic Interventions

Yujeong Song[1], Jeong-Oh Shin[1]

[1]*Department of Anatomy, Soonchunhyang University College of Medicine*

Abstract : Chemotherapy-induced mucositis (CIM) is a significant and often severe complication of cancer treatment, characterized by inflammation and ulceration of the mucosal lining throughout the gastrointestinal tract. This debilitating condition not only severely impacts patient quality of life by causing pain, difficulty eating, and increased risk of infection, but also frequently necessitates dose reductions or treatment interruptions, ultimately affecting overall treatment outcomes. This review summarizes the pathophysiological mechanisms underlying CIM, emphasizing the essential roles of reactive oxygen species (ROS), inflammation, inflammasome activation, and cellular organelle dysfunction. The main molecular mediators involved, such as ROS, proinflammatory cytokines, and NLRP3 inflammasome, and potential therapeutic interventions targeting these pathways are discussed. We will carefully review the successive phases in the evolution of mucositis, from epithelial insult to progression and ulceration to healing. This review discusses the primary molecular mediators involved: ROS, proinflammatory cytokines, transcription factor NF-κB, NLRP3 inflammasome, mitochondria, and endoplasmic reticulum (ER) stress. We also explore the therapeutic landscape and discuss potential interventions against these key pathways, followed by discussing future steps to improve CIM management. This review aims to comprehensively analyze the therapeutic landscape and propose targeted interventions against key pathways involved in CIM, ultimately outlining future strategies to significantly improve CIM management.

Keywords : Chemotherapy, Mucositis, ROS, Inflammation, Inflammasome, Mitochondria, ER stress, Oxidative stress

INTRODUCTION

Chemotherapy remains a foundational pharmacological agent and is utilized as a first-line treatment for a multitude of malignant tumors [1]. Nonetheless, its therapeutic utility is frequently hampered by a range of adverse effects, among which chemotherapy-induced mucositis (CIM) is a prevalent complication [2]. CIM is characterized by inflammation and ulceration of the mucosal lining of the gastrointestinal (GI) tract and occurs in a significant proportion of patients receiving chemotherapy [3]. Epidemiological studies have shown that mucositis is among the most common

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Correspondence to: Jeong-Oh Shin (Department of Anatomy, Soonchunhyang University College of Medicine, Cheonan 33151, Republic of Korea)
E-mail: shinjo@sch.ac.kr

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complications, as its incidence can vary significantly with the chemotherapy used and consistently affects both the oral and intestinal mucosa [4]. Clinically, mucositis presents as a constellation of debilitating symptoms, including, but not limited to, oral pain, dysphagia, and diarrhea. In severe presentations, the disease may progress to dehydration, malnutrition, and an increased risk of systemic infections [5]. In addition to early suffering, CIM adversely affects patients' well-being and increases morbidity, CIM often requires dose reduction or for the planned course of chemotherapy to be stopped altogether. Because mucositis can lead to adjustments in treatment that are meant to minimize its severity, these changes can hinder the effectiveness of cancer treatment, highlighting the clinical relevance and difficulty of this condition for management. Hence, elucidating the mechanisms responsible for CIM is crucial for developing effective preventive and therapeutic approaches.

Through years of research, much work has been conducted to elucidate the complex pathophysiology of CIM. Previous studies have revealed multiple molecular contributors involved in the onset, progression, and resolution of mucositis. Critical factors among these include reactive oxygen species (ROS), a constellation of inflammatory mediators, and inflammasome activation [1,3,6]. In addition, growing evidence links functional defects in organelles, including the mitochondria and endoplasmic reticulum (ER), with increased cellular stress and damage in mucosal tissues [6,7]. As crucial organelles for cellular homeostasis, mitophagy seems to be the predominant target and pathway involved in the pathogenesis of CIM [8].

This review summarizes the current knowledge of CIM pathophysiology. We focused on ROS, inflammation, inflammasome activation, and cellular organelle damage-integrated synergistic effects in this complex mechanism. We will detail the stepwise evolution of mucositis, the sources and diverse actions of ROS, the complex inflammatory pathways involved, the impact of mitochondrial dysfunction, and the potential outcome of targeting contributing mechanistic entities. The scope of this review intentionally covers both oral and intestinal mucositis to emphasize the common underlying molecular mechanisms while recognizing tissue-specific nuances. This comprehensive review seeks to bring together and synthesize recent literature on CIM to inform better strategies for its prevention and management.

PATHOPHYSIOLOGY OF CHEMOTHERAPY-INDUCED MUCOSITIS

CIM is triggered by direct contact between mucosal epithelial cells and cytotoxic chemotherapeutic agents. These agents, which are designed to target cancer cells diversifying at such a fast clip, have imperfect specificity and target other rapidly dividing cells in the body, such as epithelial cells, along the GI tract [1]. The development of CIM is not an event but a dynamic and progressive process, which can be roughly divided into a few stages that may overlap. This staged progression mirrors the temporal dynamics of tissue injury and host repair to chemotherapy insults [3,9]. It is vital to understand these stages to effectively plan interventions at each stage of CIM progression. CIM is a dynamic process comprising four stages: initiation, amplification, ulceration, and healing (Fig. 1). The initiation stage involves DNA damage and ROS production, which triggers cellular stress responses. The amplification stage is characterized by the release of proinflammatory cytokines and activation of inflammasomes, leading to tissue injury. The ulceration stage involves epithelial barrier breakdown and ulcer development, increasing the infection risk. The healing stage involves inflammation resolution, tissue repair, and restoration of mucosal integrity. Chemotherapy causes cellular injury primarily through direct DNA damage to the mucosal epithelium. Simultaneously, this exposure produces ROS, initiating events that give mucositis a defined pathogenesis. This initiation phase is marked by the first molecular response to chemotherapy and the development of cellular stress (Fig. 1) [2,3].

Primary damage response: Mucosal cells initiate a response to primary damage, which is defined as DNA lesions and ROS production (Fig. 1). During this phase, mucosal tissue activates an array of cellular stress pathways to limit the initial injury [3]. Several transcription factors participate in this process, including nuclear factor-kappa B (NF-κB) and nuclear factor erythroid 2-related factor 2 (Nrf2). In particular, activation of Nrf2 was initially linked to an effort to initiate an antioxidant and cytoprotective response to balance oxidative stress and cellular damage [10]. Nevertheless, the massive oxidative and cytotoxic stress induced during chemotherapy is frequently too high for these endogenous defensive systems to handle, resulting in an abnormal state that is proinflammatory instead of protective [11]. This initial damage response is characterized by

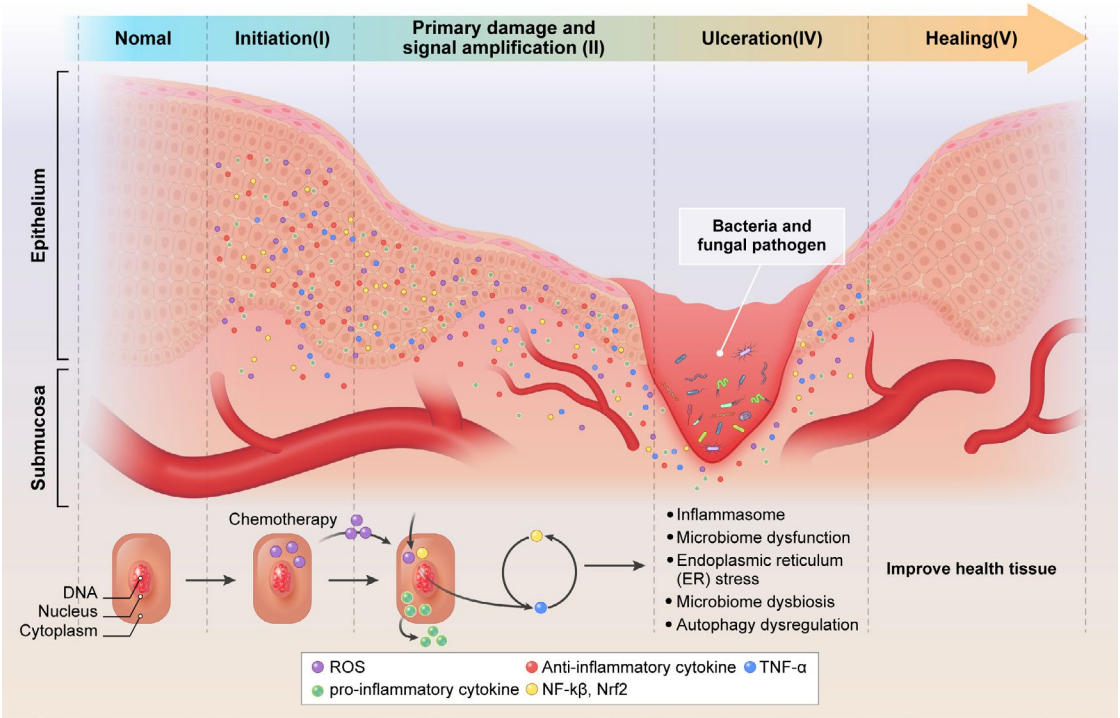

Fig. 1. Overview of the pathobiology of chemotherapy-induced mucositis (CIM).

the early upregulation and release of a range of inflammatory mediators, indicating that initiating an inflammatory cascade is critical in the pathogenesis of mucositis.

The primary damage response smoothly transitions into a signal amplification phase, in which local cellular distress gives way to a global inflammatory response. This amplification is primarily due to the release of proinflammatory cytokines from both injured epithelial cells and immune cells that begin to infiltrate the mucosal tissue. Recognition of DAMPs and PAMPs by various cell types initiates the second stage, wherein proinflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are released in large amounts [2,6,10]. These cytokines work synergistically to enhance the inflammatory cascade, recruit immune cells to the injury site, and worsen tissue injury. Signal amplification critically depends on inflammasome activation, most notably the NLRP3 inflammasome complex [6]. The NLRP3 inflammasome is a major intracellular sensor that drives the cleavage and secretion of mature IL-1β when activated, thereby amplifying the proinflammatory cascade and sustaining the cycle of tissue damage and inflammation [6].

Mucositis progresses to ulceration as the inflammatory response becomes exacerbated and tissue damage is compounded (Fig. 1). During this stage, the epithelial barrier deteriorates and ulcers develop in the mucosal lining. This damages the protective mucosal barrier, which blocks the uptake of pathogens and irritants [3]. This breakdown of barrier integrity enables bacteria and other microorganisms from the oral cavity or intestinal lumen to infiltrate submucosal tissues [12]. Secondary infections with bacterial and fungal pathogens are frequently observed during mucosal ulceration. In addition to complicating the clinical picture, these infections may have systemic implications, worsen the patient's condition, and possibly impact the overall prognosis [13]. Ulceration stage: The ulceration stage of mucositis is a critical point in a patient's disease and is associated with considerable patient discomfort and the potential for serious sequelae [9].

Without additional cycles of chemotherapy or effective therapeutic measures, mucositis can enter the healing phase (Fig. 1). Restoration of vascular function and resolution of the acute inflammatory response, clearance of necrotic tissue and cellular debris from ulcerated sites, and initiation of tissue regeneration processes collectively comprise this final stage [2]. The release of various growth factors and repar-

ative cytokines further signals the requirement for tissue repair. It promotes proliferation and differentiation of epithelial cells to restore the integrity of the mucosal lining [3]. It is worth noting that the road to healing has not always been full or linear. Further, mucosal tissue injury may be caused by repeated cycles of chemotherapeutic administration, resulting in a persistent chronic inflammatory state of mucositis. Chronic mucositis can occur because of unresolved healing, chronic inflammation, and tissue remodeling, which pose persistent challenges to patients and clinicians [14]. Thus, the healing phase reflects an attempt by the body to repair the integrity of the mucosa, but the mercy of net benefits hides its success in terms of the overall health status of the patient, the intensity and duration of chemotherapy, and the effectiveness of supportive care measures [1].

ROS AND OXIDATIVE STRESS IN MUCOSITIS

ROS are well recognized as byproducts of cellular metabolism but are held in increasing esteem as central players in the pathogenesis of CIM [9]. ROS play a dual role as upstream triggers and key tissue damage and inflammation determinants, leading to a multistep response contributing to mucosal injury [15]. ROS are being explored in the context of chemotherapy, with a clear benefit of understanding their sources and downstream effects leading to specific drugs. ROS are reactive chemical species comprising oxygen, a part of aerobic life at the most primitive level. Nevertheless, when their production is dysregulated and surpasses the capacity of cellular antioxidant defenses, oxidative stress occurs, altering the cellular redox homeostasis and contributing to various pathological conditions, as CIM is one of them [11,16]. Through multiple pathways, chemotherapy strongly induces ROS in mucosal tissues, causing oxidative stress at the core of mucositis development [11].

1. Sources of ROS in chemotherapy-induced mucositis

Mitochondrial dysfunction is a significant source of ROS in CIM. The direct toxic effects of chemotherapeutic agents on mitochondria and cellular powerhouses are well known, as they primarily target cancerous cells. These effects result in mitochondrial dysfunction, marked by defects in the electron transport chain (ETC) and bioenergetics [16]. The ETC, an essential component of adenosine triphosphate (ATP) generation via oxidative phosphorylation, is less effective when the mitochondria are compromised. Such inefficiency leads to an increased "leakage" of electrons along the ETC, where excessive generation of superoxide radicals ($O2^{\bullet -}$), one of the significant primary ROS, occurs [11]. The consequent mitochondria-derived ROS generation leads to direct oxidative stress in mucosal cells and further worsens mitochondrial damage, leading to a vicious cycle. This ongoing cycle of mitochondrial dysfunction and ROS overproduction causes cellular stress and tissue injury during mucositis [16]. Consequently, during CIM, the mitochondria switch from energy suppliers to an essential source of oxidative damage.

NADPH oxidases (NOXs) are a family of enzymes that are significant sources of ROS during CIM. NOXs are membrane-associated enzyme complexes that catalyze NADPH-dependent superoxide radical generation from molecular oxygen [17]. Chemotherapeutic agents and inflammatory cytokines released upon exposure to a chemotherapeutic agent also serve as potent activators of NOX enzymes in mucosal and immune cells that infiltrate inflamed mucosa [18]. This activation, in turn, causes elevated ROS production in the external environment and oxidative overload in mucosal tissue. NOX-derived ROS are cytotoxic waste products that play significant roles in intracellular signaling pathways, especially those related to the amplification of inflammation [17]. NOXs modulate intercellular signaling primarily by providing extracellular ROS, which can serve as mediators to enhance the propagation and maintenance of the inflammatory response in mucositis [17,18].

A second important source of ROS in CIM is myeloperoxidase (MPO), an enzyme secreted by neutrophils, an immune cell recruited to the inflamed mucosa. MPO is a heme peroxidase enzyme that catalyzes the interaction between hydrogen peroxide (H2O2) and chloride ions for the synthesis of hypochlorous acid (HOCl), a highly oxidant [19]. Bleach (HOCl) is a highly reactive toxic compound. Although MPO-derived HOCl is crucial for microbial killing and a key neutrophil function in fighting infection, excessive MPO activity and uncontrolled HOCl generation are major contributors to collateral tissue damage and heightened inflammation in mucositis [18]. In CIM, the inflammatory environment can promote inflammatory neutrophil infiltration and the release of MPO; overproduction of HOCl

and other MPO-derived reactive oxidants can drive tissue damage [18].

ER stress has been proposed to be an essential source of ROS in CIM pathogenesis. The ER is a crucial organelle involved in protein production, folding, and calcium homeostasis, with potential stress or dysfunction resulting from chemotherapeutic exposure [11]. Chemotherapeutic agents can disrupt ER homeostasis by accumulating unfolded or misfolded proteins in the ER lumen [7]. This results in a state known as ER stress, which activates the unfolded protein response (UPR), a complex network of intracellular signaling pathways that aims to re-establish ER homeostasis [20]. Interestingly, ER stress can also initiate ROS production as a byproduct of protein misfolding and UPR signaling. In summary, ROS production from the ER adds to oxidative stress at the cellular level and renders another level of complexity to the ROS environment in CIM [21]. Therefore, the ER can switch from a vital organelle for protein processing to a provider of oxidative stress under chemotherapy-induced conditions, contributing to mucosal damage.

2. ROS-mediated DNA and protein damage

ROS are very reactive; therefore, they can react with and damage a broad spectrum of cellular macromolecules such as lipids, DNA, and proteins [22]. ROS-mediated damage to these biomolecules in CIM is a key pathophysiological phenomenon in mucosal injury [9].

Lipid peroxidation is a significant form of ROS-induced damage, with the reaction of ROS with PUFAs embedded in biological membranes being a prominent initiation event in ROS-mediated damage. PUFAs are abundant in cell membranes and, thus, are particularly susceptible to oxidative stress [23]. ROS can abstract hydrogen atoms from PUFAs, thereby triggering a cascade of reactions that results in the formation of lipid hydroperoxides and other lipid peroxidation products, including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). The loss of membrane integrity and increase in membrane permeability due to lipid peroxidation damages cells and can ultimately lead to cell death. Disruption of cellular compartmentalization, ion gradients, and homeostasis due to this compromise in membrane function ultimately leads [23].

3. ROS as a trigger for inflammatory signaling

In addition to their direct on-target cytotoxic effects, ROS also act as crucial signaling molecules that promote the activation of major inflammatory pathways that are central to CIM pathobiology. ROS are essential activators and amplifiers of inflammatory responses in mucosal tissues [24].

One of the most crucial inflammatory signaling events stimulated by ROS in CIM is NF-κB activation. NF-κB is a major transcription factor that acts as a master regulator of the expression of many proinflammatory genes [9]. The NF-κB signaling pathway can directly sense upstream ROS signals. When activated, NF-κB translocates to the nucleus and initiates the transcription of numerous genes responsible for producing proinflammatory cytokines (including TNF-α, IL-6, and IL-1β), chemokines (including MCP-1 and IL-8), adhesion molecules (including ICAM-1 and VCAM-1), and inflammatory enzymes (such as COX-2 and iNOS) [10]. The transcriptional activation of NF-κB drives the production and release of inflammatory mediators, thereby perpetuating the inflammatory cascade of mucositis. One major pathway for the association between oxidative stress and inflammation in CIM is NOX-derived ROS-mediated activation of NF-κB [6,17].

Intracellularly, ROS activates the NLRP3 inflammasome, which is an important event in CIM-cell ROS-independent inflammatory signaling. The NLRP3 inflammasome is a multiprotein complex that is a major sensor of cellular stress and danger signals [25]. ROS leads to activation of the NLRP3 inflammasome [10,26]. The NLRP3 inflammasome assembles in cells in response to ROS and other stimuli, activating caspase-1. Both interleukins are released from their inactive precursor pro-IL-1β in a proteolytic manner through caspase-1 cleavage, which generates bioactive IL-1β. Mature IL-1β is subsequently released from cells to amplify inflammation [24]. Overall, ROS-induced activation of the NLRP3 inflammasome and IL-1β release are essential pathways for oxidative stress to promote inflammatory responses in mucositis.

ROS activates both the NF-κB and NLRP3 inflammasome pathways in CIM. This dual activation increases major proinflammatory cytokines such as IL-1β, IL-6, and TNF-α [26]. Then, indirectly, but to a great extent, signaling pathways are activated by ROS, leading to the upregulation and/or release of these cytokines. IL-1β, IL-6, and TNF-α are potent proinflammatory cytokines with multicellular effects on epithelial, immune, and endothelial cell types within the mucosal tissue, further propagating the inflammatory cascade and contributing to mucositis-related tissue injury. These

cytokines drive several inflammatory effects such as blood vessel permeability, immune cell recruitment, tissue repair, and pain sensitization [16]. This upregulation of cytokines mediated by ROS activation is the primary mechanism through which oxidative stress drives inflammation and tissue injury in CIM [15,16].

INFLAMMATORY PATHWAYS IN MUCOSITIS

Mucositis is characterized by a profound inflammatory response orchestrated by complex networks of associated signaling pathways and interconnected cytokine networks [27]. Mucositis is an increasingly complex and interwoven network of interactions between diverse inflammatory pathways and cell types that collaboratively shape tissue injury and clinical manifestations rather than a simple linear paradigm of cascading events. Understanding these pathways and their crosstalk is vital for developing targeted anti-inflammatory therapeutics.

1. NF-κB signaling and proinflammatory cytokines

As described earlier, the NF-κB signaling pathway is centrally activated in CIM and is mainly triggered by chemotherapy-induced ROS and DNA damage. This signaling pathway is a master regulator of inflammation, and its activation promotes a global transcriptional response that defines the inflammatory cytokine environment associated with mucositis [10]. NF-κB is phosphorylated and translocated to the nucleus when activated by upstream signals including ROS, DNA damage, and proinflammatory cytokines. After entering the nucleus, NF-κB attaches to the promoter regions of its target genes through specific DNA sequences and induces their transcription. NF-κB has an enormous transcriptional scope, controlling genes encoding proinflammatory cytokines, chemokines, adhesion molecules, inflammatory enzymes, and other mediators that participate in the initiation and development of inflammation [10]. This drives NF-κB to produce primary inflammatory mediators in the CIM pathogenic cascade.

NF-κB upregulates several proinflammatory cytokines, including TNF-α, IL-6, and IL-1β, which are involved in mucositis [10]. TNF-α is a pleiotropic cytokine that exerts a broad spectrum of mucositis-related inflammatory effects. It induces epithelial cell apoptosis, makes the vasculature permeable, and induces other proinflammatory cytokines and chemokines [27]. Therefore, TNF-α signaling is central to CIM tissue damage and inflammatory amplification. Another critical cytokine, IL-6, also plays a role in local and systemic inflammation in mucositis [28]. IL-6 promotes inflammation and facilitates immune cell recruitment. Systemically, IL-6 is a primary stimulator of the acute-phase response and has been implicated in the natural symptoms of mucositis, such as fever and fatigue. Notably, IL-1β, a particularly potent proinflammatory cytokine, orchestrates the inflammatory pathology of CIM [27]. As described above, IL-1β is predominantly processed and released following NLRP3 inflammasome activation, which is also induced by chemotherapy and ROS [28]. IL-1β plays various proinflammatory roles in mucositis, such as vasodilation, neutrophil infiltration, and pain sensitization. It significantly mediates mucosal ulceration and tissue injury [24]. Collectively, TNF-α, IL-6, and IL-1β signaling, which are upregulated downstream of NF-κB, coordinate to exert a robust proinflammatory milieu in mucositis.

Novel evidence shows that epithelial-mesenchymal transition (EMT) may play a role in chronic inflammation in mucositis [29]. EMT is a biological process in which epithelial cells lose their epithelial characteristics and acquire mesenchymal-like features. Although EMT is critical for development and wound healing, during chronic inflammatory conditions such as CIM, it often participates in remodeling, fibrosis, and persistent dysfunction [30]. Growth factors released by inflammatory cytokines (such as TNF-α, IL-6, and ROS) can lead to EMT in mucosal epithelial cells. Vascular activation can also result in changes in cell adhesion, increased cell motility, and matrix component production, all of which have the potential to lead to chronic inflammation and tissue fibrosis, and can mediate the long-term impact of repeated or prolonged exposure to mucositis [30]. Ongoing studies have focused on EMT's impact of EMT on CIM's long-term pathology [30].

2. Inflammasome activation in mucositis

Inflammasome activation, particularly that of NLRP3 inflammasome, is an integral part of the inflammatory cascade in CIM. Inflammasomes are multiprotein complexes that serve as intracellular danger signal sensors and trigger inflammatory responses through the activation of caspase-1,

which converts pro-IL-1β into its mature form. The most studied inflammasome, NLRP3 inflammasome, is implicated in the pathogenesis of several inflammatory-related diseases, including CIM [6,31]. Chemotherapy-associated stimuli of different natures can activate NLRP3 in the mucosal and infiltrating immune cells. As mentioned previously, ROS are among these stimuli [6]. The stress generated by chemotherapy-induced cellular stress, such as ER stress and mitochondrial perturbation, can also trigger NLRP3 inflammasome activation [32]. Moreover, chemotherapy-induced dysbiosis can play a pivotal role in inflammasome activation in the intestinal mucosa, with altered gut microbial composition due to increased gut permeability, facilitating the translocation of microbial products that serve as inflammasome activators [13].

Upon activation, NLRP3 must be assembled into a cytoplasmic multiprotein complex known as the NLRP3 inflammasome, which consists of NLRP3, an adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC), and caspase-1. Caspase-1 is activated in the assembled inflammasome complex [25]. Caspase-1 is a cysteine protease that cleaves pro-IL-1β, a zymogen of IL-1β, into a highly active form. Mature IL-1β is secreted from cells to carry out its proinflammatory activity. Therefore, the NLRP3 inflammasome-caspase-1-IL-1β pathway is a key axis of inflammatory signaling in CIM. Activation of this pathway amplifies the inflammatory response and tissue injury [31].

The interplay between the gut microbiota and inflammasome activation is highly relevant in chemotherapy-induced intestinal mucositis. Antineoplastic agents that alter the gut microbiota are part of this process, and dysbiosis, defined as altered microbial composition and decreased microbial diversity, is a common consequence of chemotherapy [33]. Dysbiosis can enhance inflammation in the intestine and promote inflammasome activation via several mechanisms. Altered gut microflora may augment gut permeability by contaminating bacterial products, such as lipopolysaccharide (LPS) and peptidoglycan, through the mucosal barrier. These microbial byproducts serve as pathogen-associated molecular patterns (PAMPs) that bind to pattern recognition receptors such as Toll-like receptors (TLRs) on mucosal and immune cells, promoting NF-κB activation and NLRP3 inflammasome priming [33]. Furthermore, bacterial invasion (due to ulceration when the mucosal barrier is compromised) can deliver HALs and PAMPs and cause direct activation of inflammasomes, with consequent aggravation of inflammation and secondary infections [34]. Therefore, the gut microbiota and its interactions with the inflammasome system play a complex and significant role in the pathogenesis of chemotherapy-induced intestinal mucositis.

3. Crosstalk between inflammation and cell death pathways

CIM does not represent a mutually exclusive process involving inflammation or cell death pathways. Instead, they are not only intimately associated but also often cooperatively mediate mucosal injuries. TNF-α and IL-1β are examples of inflammatory signals that can directly drive different modes of regulated cell death, whereas cell death processes can release danger signals that amplify inflammation [27]. This crosstalk between the inflammation and cell death pathways is a hallmark of CIM pathophysiology [28].

Intrinsic and extrinsic pathways may trigger apoptosis or programmed cell death type I, one of the primary forms of regulated cell death in mucositis [35]. The intrinsic apoptotic pathway, or mitochondrial pathway, is stimulated by cellular stresses, such as DNA damage, oxidative stress, and mitochondrial dysfunction, all of which are features of CIM. Stress signals activate the permeabilization of the mitochondrial outer membrane and the release of cytochrome c into the cytoplasm from the mitochondrial intramembranous space. Cytoplasmic cytochrome c subsequently engages the caspase cascade, a series of proteolytic processes involving initiator caspases (e.g., caspase-9) and executioner caspases (e.g., caspase-3 and caspase-7), culminating in cellular dismantling and apoptosis [35]. Death ligands, such as TNF-α and Fas ligand (FasL), bind to death receptors (e.g., TNFR1 and Fas receptor) on the cell surface to activate the extrinsic apoptotic pathway. Ligation of this receptor induces activation of initiator caspases (e.g., caspase-8), which activate downstream apoptotic cascades and promote apoptosis [35]. Both the death receptor-mediated (extrinsic) and mitochondrial (intrinsic) apoptotic pathways are involved in the loss of epithelial cells in mucositis, and increased activation of these pathways is often interconnected and synergistic in the setting of CIM.

Pyroptosis, also known as programmed cell death type II, is an inflammatory form of programmed cell death controlled by inflammasome activation and gastrin D. It differs from apoptosis, whereby pyroptosis involves cell swelling, rupture of plasma membranes, expulsion of proinflamma-

tory intracellular contents, and loss of cells [36]. Pyroptosis in CIM is induced mainly by NLRP3 inflammasome activation. Following NLRP3 inflammasome activation and caspase-1 processing, caspase-1 cleaves gasdermin D, a pore-forming protein, thereby releasing its N-terminal domain. Gasdermin D oligomerizes into pores in the plasma membrane via its N-terminal domain [26]. These pores compromise the integrity of cellular membranes, resulting in cellular swelling and osmotic lysis, and the release of proinflammatory cytokines and intracellular molecules, of which IL-1β and alarmins are expelled into the extracellular space. The release of proinflammatory molecules from immune cells also causes tissue inflammation [28]. Pyroptosis is an inflammatory cell death mechanism that plays a role in CIM epithelial cell death and inflammatory amplification [36].

Another type of regulated cell death is necroptosis, which can be activated in the context of "inflammatory" conditions and has implications in CIM pathogenesis [36]. Unlike apoptosis and pyroptosis, necroptosis has unique morphological and biochemical characteristics. It is mediated through a signaling cascade involving receptor-interacting protein kinase 1 (RIPK1), RIPK3, and mixed-lineage kinase domain-like pseudokinase (MLKL) [36]. Necroptosis pathways have also been activated in mucositis but can only be triggered by TNF-α signaling when apoptosis is inhibited, that is, by caspase inhibitors [35]. After necroptosis signaling is activated, RIPK1 and RIPK3 are phosphorylated and activated, forming a necrosome complex that phosphorylates and activates MLKL. Upon activation, MLKL oligomerizes and embeds into the plasma membrane, causing membrane permeability and cell lysis, hallmarks of necroptosis [36]. Necroptosis, similar to pyroptosis, is an inflammatory form of cell death that releases intracellular contents, further triggering inflammation. Mucositis-mediated activation of necroptosis pathways contributes to epithelial cell loss and inflammation and may be particularly relevant under conditions where apoptosis is inhibited or insufficient [36].

CELLULAR ORGANELLE DYSFUNCTION IN MUCOSITIS

Dysfunction of cellular organelles, particularly the mitochondria, ER, and autophagy, is emerging as a critical factor in the pathogenesis of CIM [7]. These organelles play a pivotal role in cellular homeostasis and function and are significant targets and mediators of cellular damage occurring in CIM. This dysfunction leads to cell stress, exacerbates cell stress, disrupts energy metabolism, and causes inflammation and cell death [21].

1. Mitochondrial dysfunction

Mitochondrial dysfunction is a defining characteristic of CIM pathophysiology. As described above, chemotherapeutic drugs are introduced into the mitochondria and elicit a cascade of deleterious effects on their morphology and function. Such chemotherapy-induced damage to mitochondria contributes to ROS overproduction, which initiates and amplifies mucositis [15]. Mitochondria exhibit impaired ATP production capacity, resulting in the depletion of cellular energy. ATP, the basic cellular energy carrier, is required for almost all cellular functions. Mitochondrial dysfunction and resultant ATP depletion impair cellular function throughout the body and can lead to cell death in mucositis. Thus, mitochondrial dysfunction leads to oxidative stress and causes cell energy deprivation, which aggravates cellular injury [8].

Opening of the mitochondrial permeability transition pore (mPTP) is an essential mitochondrial dysfunction mechanism induced by CIM. The mPTP is a channel formed by the components of the mitochondrial inner membrane that, when activated, causes permeability transition, leading to mitochondrial membrane permeabilization. Calcium overload and oxidative stress are mitochondrial dysfunctions that induce mPTP opening [8]. Opening of the mPTP compromises $\Delta\Psi m$, which is critical for ATP generation. This leads to the release of cytochrome c from the intermembrane space of the mitochondria into the cytoplasm, activating the intrinsic apoptotic pathway [37]. Moreover, mPTP opening was responsible for mitochondrial swelling and the widespread collapse of mitochondrial structural and functional integrity. Therefore, mPTP opening is a key event in mitochondrial dysfunction and contributes to ATP depletion, apoptosis, and mitochondrial damage in CIM [37].

Mitophagy, a cellular quality-control mechanism in which damaged mitochondria are removed by autophagy, is dysregulated in CIM. Mitophagy is critical for maintaining a healthy mitochondrial pool by removing damaged mitochondria and preventing their accumulation to avoid their contribution to stress, as would be the case in a vicious cycle [37]. Mitophagy is associated with both cytoprotection

and cell injury depending on the stage and context of CIM. Mitochondrial clearance can also be restricted in the early phases of mucositis, thereby reducing ROS downscaling and cellular stress by eliminating ruptured mitochondria [8]. In contrast, mitophagy may become excessive or defective at later stages or advanced levels of mitochondrial damage. Excessive mitophagy depletes the mitochondrial pool and impairs cellular energy generation and function. Conversely, inhibition of mitophagy may result in the aggregation of injured mitochondria, worsening of mitochondrial impairment, and oxidative stress [37]. In CIM, mitochondrial biogenesis—a new mitochondrial generation—can be impaired and unable to replenish the damaged mitochondrial pool. Mitochondrial dysfunction and subsequent cell injury involved in mucositis are associated with dysregulation of both mitophagy and mitochondrial biogenesis [8].

2. Endoplasmic reticulum stress

Another prominent feature of cellular organelle dysfunction in CIM is ER stress. The ER, an organelle responsible for protein synthesis, folding, and calcium homeostasis, is particularly sensitive to chemotherapy-induced cellular stress. ER homeostasis can be perturbed by chemotherapeutic agents, resulting in the accumulation of unfolded or misfolded proteins in the ER lumen, which is referred to as ER stress [7]. ER stress activates the UPR, a complex intracellular signaling network that recovers ER homeostasis. UPR is an acute pro-survival response that alleviates ER stress by increasing the folding capacity of the ER, attenuating the load of protein synthesis in the ER, and increasing ER-associated degradation (ERAD) of misfolded proteins [7,20].

However, if ER stress is prolonged or severe, and the UPR cannot restore ER homeostasis, the UPR can shift from pro-survival to pro-apoptotic signaling. Key UPR pathways, mediated by C/EBP-homologous protein (CHOP), protein kinase RNA-like ER kinase (PERK), and activating transcription factor 4 (ATF4), can induce apoptotic pathways that can contribute to ER stress-mediated cell death in mucositis [20]. CHOP is an example of a pro-apoptotic transcription factor whose expression is induced by ER stress, which promotes apoptosis through the enhanced expression of pro-apoptotic genes and reduced expression of anti-apoptotic genes. Upon activation by ER stress, it phosphorylates eIF2α (eukaryotic initiation factor 2α), leading to a global decrease in protein synthesis to reduce the ER protein folding burden; initially, persistent eIF2α phosphorylation can also promote pro-apoptotic pathways [7]. Another ER stress-activated transcription factor, ATF4, can promote pro-survival versus pro-apoptotic genes, depending on the duration and severity of ER stress [21]. Thus, ER stress and the UPR are complex cellular stress responses that can lead to cell survival and death in CIM.

The ER and mitochondria do not exist as isolated organelles; they are physically and functionally interdependent and engage in ER-mitochondria contact sites (also referred to as mitochondria-associated ER membranes [MAMs]) [7]. ER-mitochondrial contact sites enable crosstalk between these organelles and are involved in calcium homeostasis, lipid metabolism, and mitochondrial function. In CIM, ER stress and mitochondrial dysfunction mutually exacerbate each other through ER-mitochondrial crosstalk. Mitochondrial dysfunction and ROS can drive ER stress and vice versa. As a result, ER stress can stimulate calcium overstimulation from the ER, which can cause mitochondrial calcium overload and the opening of the mPTP and aggravate mitochondrial dysfunction [7,8]. Mitochondrial ROS production may also induce direct injury to the ER, exacerbating ER stress. This ER-mitochondria crosstalk amplifies oxidative damage and cellular injury in CIM [7].

3. Autophagy dysregulation

Autophagy, a cellular self-digestion pathway characterized by lysosomal degradation of cytoplasmic proteins, is involved in mucositis in a complex and context-specific manner [35]. Autophagy is an evolutionarily conserved cellular process necessary for cellular homeostasis and stress responses. In CIM, autophagy can be either protective or destructive, and its overall contribution to mucositis pathogenesis is complex and unclear. In the initial phase of CIM, removing damaged organelles, such as damaged mitochondria (mitophagy) and ER (ER-phagy), and digesting cellular debris can inhibit autophagy, thus inducing cellular survival and mucosal healing. In addition, autophagy degrades intracellular pathogens and inflammatory mediators, thereby inhibiting inflammation [37,38].

Aberrantly elevated or dysregulated autophagy disrupts mucositis, leading to cell death and tissue injury. However, in some instances, autophagy can promote cell death, which is termed autophagic or type II programmed cell death. Excessive autophagy can damage cellular functions by

breaking down essential organelles but can also induce cell death [39]. Disruption of autophagy can potentially hinder the normal functions of cells and their repair mechanisms. Autophagy has protective versus destructive roles in mucosal healing in CIM, which are likely context-dependent and vary with mucositis stage, chemotherapy intensity, and additional factors.

The interplay between autophagy and inflammasome activation is also pertinent to CIM. Autophagy and inflammasomes are two major cellular pathways involved in cellular stress and inflammation and are increasingly appreciated for their interaction with one another. Autophagy negatively regulates inflammasome activation, and is a negative feedback mechanism that regulates excessive inflammation [39]. Autophagy has been shown to degrade inflammasome components, including NLRP3 and caspase-1, and remove damaged mitochondria, a significant source of inflammasome-activating stimuli, curbing inflammasome activation [40]. In contrast, activation of the inflammasome can alter autophagic flux, possibly by stimulating and inhibiting autophagy, depending on the context [6]. Further investigation into the exact aspects of autophagy-inflammasome crosstalk in CIM and how they modify its development will provide deeper insights into the significance of autophagy in CIM pathogenesis and whether autophagy-modulating therapeutic strategies are worth exploring.

THERAPEUTIC INTERVENTIONS TARGETING ROS AND INFLAMMATION

The involvement of ROS and inflammation in the underlying mechanism of CIM, along with the impact of chemotherapy on cellular organelles, as described in this review, highlights the possible therapeutic strategies that need to be developed to target these key pathways for the prevention and treatment of this debilitating condition. It is likely that the management of CIM is best achieved through a multifaceted therapeutic approach that can alleviate oxidative stress, inflammation, and organelle dysfunction.

1. Antioxidants and ROS scavengers

Antioxidants and ROS scavengers constitute an intuitive therapeutic strategy to address oxidative stress, a central pathogenic factor in CIM. N-acetylcysteine (NAC), a precursor of the endogenous antioxidant glutathione, is extensively used as a mucolytic agent with antioxidant properties. NAC can also increase cellular levels of glutathione, which increases cellular antioxidant capacity and directly scavenges ROS [41]. Clinical studies have shown that the administration of NAC may have a protective effect on the severity and duration of mucositis. Superoxide dismutase (SOD) mimetics (e.g., manganese porphyrins (MnTBAPs)) are synthetic SOD mimetics that catalyze the dismutation of superoxide radicals, one of the most critical ROS [1]. NAC scavenges ROS in a more indirect manner than SOD mimetics, which directly scavenge superoxide radicals. These substances, NAC and SOD mimetics, may alleviate oxidative stress and tissue damage in mucositis, helping relieve symptoms and promote mucosal recovery [41].

Mitochondria-targeted antioxidants, such as MitoQ and SkQ1, provide a more refined antioxidant therapy. These compounds are synthesized to selectively accumulate in the mitochondria, the major source of intracellular ROS under CIM, and scavenge ROS at the site of ROS generation [8]. MitoQ is a ubiquinone derivative conjugated to a lipophilic triphenylphosphonium cation, which allows for its accumulation in the mitochondria owing to its negative mitochondrial membrane potential [8]. SkQ1 is a plastoquinone derivative conjugated to a decyl triphenylphosphonium cation that behaves similarly to target mitochondria. These mitochondria-targeted antioxidants can protect the mitochondria from oxidative damage by neutralizing mitochondrial ROS production, reducing cellular oxidative stress, and improving mitochondrial function in mucositis. Therefore, they may provide better therapeutic efficacy than general antioxidants [8].

2. Anti-inflammatory therapies

Anti-inflammatory therapies are also a key pillar of CIMs therapeutic management and benefit from the prominent role of inflammation in its pathogenesis. Proinflammatory cytokines, such as IL-1β and TNF-α, are paramount to the inflammatory response that engenders mucositis; thus, the neutralization of IL-1β and TNF-α is a logical target for therapeutic manipulation. IL-1β can be targeted therapeutically by blocking its receptor (e.g., with the IL-1 receptor antagonist anakinra) or by neutralizing the cytokine itself (e.g., with the monoclonal antibody canakinumab) [42]. TNF-α inhibitors (e.g., infliximab, anti-TNF-α chimeric monoclonal antibody, etanercept, TNF-α receptor, Fc fusion protein, and adalimumab, anti-TNF-α human monoclonal

antibody) act similarly on TNF-α to suppress inflammation [43]. Such IL-1β and TNF-α antagonism has demonstrated preclinical efficacy in mucositis models and has been tested in clinical studies for the management of mucositis with mixed results [43].

Novel therapies for CIM involve NF-κB signaling pathway inhibitors as a broader strategy for anti-inflammatory treatment. As mentioned above, the NF-κB pathway is a master regulator of inflammation and directs the expression of several proinflammatory genes. As NF-κB is a promoter of multiple inflammatory mediators, inhibiting this pathway might result in a more potent anti-inflammatory effect than simply targeting single cytokines [10]. Different classes of NF-κB inhibitors have been isolated and studied, from natural compounds (e.g., curcumin and resveratrol) to synthetic molecules. These NF-κB inhibitors exert anti-inflammatory effects via various mechanisms to prevent the activation of NF-κB or NF-κB downstream signaling [10]. However, the systemic administration of broad-spectrum NF-κB inhibitors could have undesirable side effects owing to the pleiotropic properties of NF-κB in normal cellular processes; targeted delivery or local administration could be a more favorable strategy in the clinical application of NF-κB inhibitors to mucositis.

3. Targeting inflammasome activation

Since the NLRP3 inflammasome and IL-1β play critical roles in the pathogenesis of mucositis, targeting inflammasome activation, particularly the NLRP3 inflammasome, is a more specific anti-inflammatory strategy in CIM [26]. NLRP3 inflammasome inhibitors have been developed, including selective inhibitors such as MCC950 and less selective inhibitors such as glyburide. MCC950 is a small-molecule inhibitor with potent specificity for NLRP3 inflammasome activation [40]. The antidiabetic drug glyburide has also been demonstrated to inhibit NLRP3 inflammasome activation [44]. NLRP3 inhibitors have a mechanism of action to inhibit the assembly or activation of the NLRP3 inflammasome, leading to decreased caspase-1 activation and subsequent IL-1β production. In preclinical studies using animal models of mucositis, NLRP3 inhibitors have been shown to reduce the severity of mucositis, suggesting their therapeutic potential.

Inhibitors of caspase-1 provide another mechanism to mitigate inflammasome-driven inflammation in CIM. The NLRP3 inflammasome recruits and activates caspase-1, an enzyme that cleaves pro-IL-1β into its active form IL-1β. Caspase-1 inhibitors, such as VX-765 (belnacasan) and pralnacasan, can directly inhibit caspase-1 enzymatic activity, thereby blocking the generation and secretion of the active form of IL-1β. As they inhibit the production of mature IL-1β downstream of NLRP3 activation, caspase-1 inhibitors can be a more direct and selective means of inhibiting IL-1β-mediated inflammation than NLRP3 inhibitors [31]. Inhibitors of caspase-1 have demonstrated the ability to reduce mucosal inflammation in preclinical models of inflammatory diseases, and their potential in the treatment of mucositis is being investigated.

4. Modulating cellular organelle function

In CIM, modulation of cellular organelle function, including that of the mitochondrion and ER stress, constitutes a new therapeutic strategy by correcting organelle dysfunction driving mucositis pathogenesis. The creation of new healthy mitochondria can be stimulated by mitochondrial biogenesis activators such as pyrroloquinoline quinone (PQQ)3, nicotinamide riboside (NR)4, and resveratrol [45,46]. PQQ is an antioxidant quinone cofactor that promotes mitochondrial biogenesis. NR is a precursor of nicotinamide adenine dinucleotide (NAD+), a coenzyme necessary for mitochondrial function and biogenesis [46]. Resveratrol, a natural polyphenol, has been reported to promote mitochondrial biogenesis. These agents may restore mitochondrial function and improve cellular energy production by increasing mitochondrial biogenesis, reducing oxidative stress in mucositis, and promoting mucosal healing.

Another approach to modulate cellular organelle functions during CIM is ER stress modulators, such as 4-phenylbutyric acid (4-PBA) and tauroursodeoxycholic acid (TUDCA) [7]. 4-PBA is a chemical chaperone that assists in the proper folding of improperly folded proteins and therefore reduces stress inside the ER. TUDCA is a bile acid with chemical chaperone and ER stress-reducing properties [7]. Thus, by alleviating ER stress-induced cellular damage and inflammation, ER stress modulators may mitigate mucositis by restoring ER homeostasis and promoting mucosal cell survival and tissue regeneration. Targeting a major contributor to CIM pathogenesis and ER dysfunction using ER stress modulators is a potential therapeutic strategy.

5. Microbiome-based therapies

Therapies based on microbiomes, mainly probiotics and fecal microbiota transplantation (FMT), are promising and increasingly investigated therapeutic strategies for chemotherapy-induced intestinal mucositis [47]. Probiotics are live microorganisms that, when administered in sufficient quantity, confer health benefits to the host and have been shown to alter the composition of gut microbiota and decrease inflammation in mucositis [13].

Certain probiotic strains, primarily *Lactobacillus* and *Bifidobacterium*, have been found to exert beneficial effects on mucositis through several mechanisms, such as direct improvement of gut barrier function, suppression of bacterial translocation, modulation of mucosal immune responses, and production of beneficial metabolites, such as short-chain fatty acids (SCFAs) [13]. Systematic evidence from clinical trials highlights the practical benefits of probiotics in preventing chemo-induced intestinal mucositis, underscoring their potential role in supporting cancer patients undergoing chemotherapy [13]. More clinical trials with a stronger design are required to elucidate the best probiotic strains, doses, and regimens for CIM.

FMT, the transfer of fecal microbiota from a healthy donor into a recipient, is a more radical and complete approach to restoring gut microbiota homeostasis [47]. FMT seeks to restore the diversity and composition of normal gut microbiota in patients with dysbiosis-related diseases. FMT has been remarkably effective in treating recurrent *Clostridium difficile* infections and is currently being explored for its possible benefits in other GI disorders and extra-intestinal diseases related to gut microbiota dysbiosis. Rapid medications are being investigated to manage chemotherapy-induced intestinal mucositis effectively, and preliminary studies have shown good efficacy. Thus, FMT may be especially useful for severe intestinal mucositis associated with profound gut microbiota dysbiosis. Nonetheless, FMT is a complicated treatment approach, with risks that include infection transmission and immune reactions, and therefore should consist of thorough evaluation, selection, and monitoring of patients [47]. However, further studies are required to clarify the role of FMT in the treatment of patients with chemotherapy-induced intestinal mucositis, including optimal donor selection, delivery methods, and long-term outcomes.

FUTURE DIRECTIONS AND CONCLUSION

Significant progress has been made in understanding the pathophysiology of CIM, and new potential therapeutic strategies have been developed. However, prevention and management of CIM remains a considerable clinical challenge. More research is needed in the following areas to enhance our capability to counteract this debilitating complication: Some especially promising future directions include personalized medicine approaches, multi-omics studies, and nanotechnology applications for targeted drug delivery systems.

Tailoring preventive and therapeutic approaches to the distinct characteristics of individual patients with CIM through personalized medicine approaches is also critical for effectively managing CIM. CIM in individual patients may be profoundly influenced by the genetic background, gut microbiota composition, chemotherapy regimen, and other determinants, leading to variations in the incidence and severity of CIM. Future studies are needed to identify predictive biomarkers that stratify patients according to their risk of CIM and allow for differential risk-adapted preventive strategies. Moreover, tailored therapeutic strategies that consider patient- and disease-specific strategies are essential for enhancing therapeutic benefits. With access to genomic, transcriptomic, proteomic, metabolomic, and other "omics" information, multi-omics approaches constitute a powerful means of achieving a more comprehensive and systematic understanding of the intricate molecular networks involved in CIM pathogenesis [48]. Multi-omics studies allow the identification of new therapeutic targets and biomarkers for personalized risk stratification and treatment follow-up and contribute to understanding the molecular mechanisms involved in interindividual differences in susceptibility and responsiveness to CIM.

Nanotechnology-based targeted drug delivery systems are promising avenues for enhancing drug efficacy while minimizing systemic toxicity in mucositis [49]. Nanoparticles are designed to target mucosal tissues with promising approaches to directly deliver therapeutic agents to affected sites, increase drug concentration in the target tissue, and reduce off-target drug distribution and systemic toxicity. Moreover, nanoparticles may be designed for sustained drug release, resulting in prolonged therapeutic effects owing to the reduced frequency of administration. Recently, nano-

technology-based drug delivery systems, such as liposomes, polymeric nanoparticles, and nanogels, have been studied for the delivery of antioxidants, anti-inflammatory agents, organelle-modulating compounds, and microbiome-modulating therapies for CIM. These nanotechnological systems provide new perspectives for developing more effective and safer CIM treatment methods.

Recent advancements in multi-omics approaches, integrating genomics, transcriptomics, proteomics, and metabolomics, hold significant promise for elucidating the complex mechanisms underlying CIM [48]. For example, single-cell transcriptomics has revealed distinct mucosal cell subpopulations that exhibit differential susceptibility to chemotherapy-induced damage [48]. These findings could guide the development of patient-specific biomarker panels for early CIM detection and risk stratification. Additionally, advancements in artificial intelligence (AI)-driven drug discovery may accelerate the identification of novel CIM therapeutics by predicting drug-mucosa interactions at the systems biology level [49].

In summary, CIM involves many factors that orchestrate complex crosstalk between ROS and inflammatory mediators and pathological changes within cellular organelles. We present approaches based on personalized medicine, multi-omics techniques, and novel drug delivery strategies that target these key pathways to improve and treat this debilitating condition. Therefore, appropriate control of CIM could improve quality of life and therapeutic outcomes in cancer patients undergoing chemotherapy.

The figure shows the stages of chemotherapy-induced mucosal ulceration and recovery. CIM occurs when cytotoxic agents damage rapidly dividing mucosal epithelial cells, triggering DNA lesions and producing ROS. This initiates a cellular stress response involving transcription factors, such as NF-κB and Nrf2, which attempt to counteract oxidative damage but often fail, leading to a proinflammatory state. The subsequent amplification phase is driven by the release of cytokines and TNF-α, with inflammasomes sustaining inflammation. As mucositis progresses, epithelial barrier breakdown results in ulceration, increased susceptibility to infections, and systemic complications. The healing phase involves vascular restoration, resolution of inflammation, and epithelial regeneration. CIM; chemotherapy-induced mucositis, ROS; reactive oxygen species, TNF-α; tumor necrosis factor-alpha, Nrf2; nuclear factor erythroid 2-related factor 2.

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