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INVITED REVIEW

Microbes mediated immunogenic cell death in cancer immunotherapy

Jumin Huang[1,2] | Fugang Duan[3,4,5] | Chun Xie[1,2] | Jiahui Xu[1,2] | Yizhong Zhang[6] | Yuwei Wang[7] | Yu-Ping Tang[7] | Elaine Lai-Han Leung[1,2,8]

[1]Cancer Center, Faculty of Health Sciences, University of Macau, Macau (SAR), China

[2]MOE Frontiers Science Center for Precision Oncology, University of Macau, Macau (SAR), China

[3]Department of Immunology, School of Basic Medical Sciences, Peking University Health Science Center, Beijing, China

[4]NHC Key Laboratory of Medical Immunology, Peking University Health Science Center, Beijing, China

[5]Key Laboratory of Molecular Immunology, Chinese Academy of Medical Sciences, Beijing, China

[6]Dr. Neher's Biophysics Laboratory for Innovative Drug Discovery, State Key Laboratory of Quality Research in Chinese Medicine, Dr. Macau Institute for Applied Research in Medicine and Health, Macau University of Science and Technology, Macau (SAR), China

[7]Key Laboratory of Shaanxi Administration of Traditional Chinese Medicine for TCM Compatibility, Shaanxi University of Chinese Medicine, Xi'an, Shaanxi Province, China

[8]State Key Laboratory of Quality Research in Chinese Medicine, University of Macau, Macau, China

Correspondence
Elaine Lai-Han Leung, Cancer Center, Faculty of Health Sciences, University of Macau, Macau (SAR), China, MOE Frontiers Science Center for Precision Oncology, University of Macau, Macau (SAR), China and State key Laboratory of Quality Research in Chinese Medicine, University of Macau, Macau, China.
Email: lhleung@um.edu.mo

Yu-Ping Tang, Key Laboratory of Shaanxi Administration of Traditional Chinese Medicine for TCM Compatibility, Shaanxi University of Chinese Medicine, Xi'an 712046, Shaanxi Province, China.
Email: yupingtang@sntcm.edu.cn

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Summary

Immunogenic cell death (ICD) is one of the 12 distinct cell death forms, which can trigger immune system to fight against cancer cells. During ICD, a number of cellular changes occur that can stimulate an immune response, including the release of molecules called damage-associated molecular patterns (DAMPs), signaling to immune cells to recognize and attack cancer cells. By virtue of their pivotal role in immune surveillance, ICD-based drug development has been a new approach to explore novel therapeutic combinations and personalized strategies in cancer therapy. Several small molecules and microbes can induce ICD-relevant signals and cause cancer cell death. In this review, we highlighted the role of microbe-mediate ICD in cancer immunotherapy and described the mechanisms through which microbes might serve as ICD inducers in cancer treatment. We also discussed current attempts to combine microbes with chemotherapy regimens or immune checkpoint inhibitors (ICIs) in the treatment of cancer patients. We surmise that manipulation of microbes may guide personalized therapeutic interventions to facilitate anticancer immune response.

KEYWORDS
cancer immunotherapy, immunogenic cell death, microbes

Jumin Huang and Fugang Duan contributed equally to this paper.

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1 | INTRODUCTION

Immunogenic cell death (ICD) represents a form of programmed cell death (PCD) in which the dying cell releases damage-associated molecular patterns (DAMPs) that can initiate an effective immune response to recognize and attack cancer cells. In 2005, the concept of ICD was first put forward and distinguished from other regulated cell deaths, such as apoptosis, necroptosis, and ferroptosis.[1] By virtue of their pivotal role in immune surveillance, ICD-based drug development has been a new approach to explore novel therapeutic combinations and personalized strategies in cancer therapy. In 2020, two ICD inducers, lurbinectedin and belantamab mafodotin, received accelerated approval from the Federal Drug Administration (FDA) for the treatment of small cell lung cancer (SCLC) and multiple myeloma.[2,3] ICD inducers need to meet three major characteristics, namely antigenicity, adjuvanticity, and a permissive microenvironment.[4,5] Indeed, several standard cancer therapies, including chemotherapy (e.g., oxaliplatin, cyclophosphamide, and anthracyclines),[6–9] radiotherapy,[10] as well as targeted anticancer agents (e.g., bortezomib and crizotinib)[11–13] have been shown to trigger ICD of cancer cells. Subsequently, the dying cancer cells activate or boost the adaptive anti-tumor immunity in support of cancer treatment.

Recently, not only these small molecular ICD inducers but also pathogen infection that can emit ICD-relevant signals are being drawn attention. Thus, a novel concept of microorganism-associated molecular patterns (MAMPs) to induce ICD opens a new era of cancer therapy and drug development strategies. Pathogen infection by microbes can generate a reservoir of antigens and exhibit sufficient antigenicity, which is capable to activate antigen-specific immune response by exposing pattern recognition receptors (PRRs). Cell wall components of bacteria including lipopolysaccharide, lipoteichoic acid, flagellin, fungal β-glucans and α-mannans, and viral nucleic acid can act as PAMPs, which are mainly recognized by diverse Toll-like receptors (TLRs) and directly activate immune cells.[14] Besides, certain specific MAMPs are found to be expressed on antigen-presenting cells, which serves as natural adjuvants and initiate the antigen-specific immune response.[15] Microbes can also promote the production of other molecules that can induce immunogenic cell death, such as reactive oxygen species (ROS) and other reactive metabolites. These molecules can then trigger the activation of caspases and other proteases, which ultimately lead to the death of the cell.

In this review, we summarized the recent novel mechanisms through which microbes might serve as ICD inducers in cancer treatment. We also discuss current attempts to combine microbes with chemotherapy regimens or immune checkpoint inhibitors (ICIs) in the treatment of cancer patients. We surmise that manipulation of microbes may guide personized therapeutic interventions to facilitate anticancer immune response.

2 | POLYMORPHIC MICROBES: A NEW EMERGING CANCER HALLMARK

Cancer is a multifaceted disease that stems from a variety of factors, including genetic mutations, environmental exposures, and lifestyle choices. Accumulating evidence supports the notion that human microbiome plays a crucial role in the development and progression of various cancers.[16,17] The polymorphic microbiome has been identified as a new cancer hallmark.[18] It has been suggested that certain microbial species may directly promote or inhibit tumor growth, while others contribute to the activation or suppression of the immune system in response to cancer. Furthermore, the polymorphic microbiome has been found to influence the efficacy and toxicity of cancer treatments, such as chemotherapy and immunotherapy. Currently, seven viruses and one bacterium have been formally identified and recognized as causative cancer agents in humans: Epstein–Barr Virus, Hepatitis B Virus, Hepatitis C Virus, Kaposi Sarcoma Herpesvirus, Human Immunodeficiency Virus-1, Human Papillomaviruses, Human T-cell Lymphotropic Virus Type 1, and *Helicobacter Pylori*.[19–21]

Beyond *Helicobacter Pylori*, recent research also indicates that dozens of bacteria are related to oncogenesis, such as *Fusobacterium nucleatum*,[22] *Bacteroides fragilis* (ETBF),[23] *Escherichia coli*,[24] and Stenotrophomonas.[25] *Fusobacterium nucleatum* commonly exists in colorectal cancer and esophageal cancer.[26] It promotes the occurrence and deterioration of tumors, inhibit the cytotoxic of NK cells[27] and tumor-infiltrating T cells,[28] and ultimately results in chemotherapy resistance of cancers.[29] *Bacteroides fragilis* can produce enterotoxin to induce colon cancer via upregulating histone demethylase JMJD2B in TLR4-NFAT5-dependent pathway.[30,31] While on the contrary, certain probiotics exert synergistic effect of chemotherapy or immunotherapy. Oral administration of *Akkermansia muciniphila* to microbiota-depleted tumor-bearing mice could restore the restore response to ICIs through the increased recruitment of $CCR9^+CXCR3^+CD4^+$ T cells into tumor microenvironment in an interleukin-12-dependent manner.[32] Intratumoral *Lactobacillus reuteri* potentiated response to ICIs in melanoma mouse models by releasing the metabolite indole-3-aldehyde, which can strongly boost $CD8^+$ T cells with the production of IFN-γ.[33] Additionally, two studies on fecal microbial transplantation (FMT) have been successfully conducted from melanoma patients who experienced a complete response to immune checkpoint inhibitors (ICIs) into resistant patients. The results showed that increased abundance of Ruminococcaceae

and Bifidobacteriaceae was associated with the improved response, providing a proof of concept that targeting gut microbiota could reverse the resistance to ICIs.[34,35] Besides, recent efforts also found that individual microbial species or microbial consortia has the potential to facilitate cancer therapies.[36,37] *Bifidobacterium pseudolongum*, *Lactobacillus johnsonii*, and *Olsenella species* were demonstrated to significantly enhance the efficacy of ICIs. The effect of *Bifidobacterium pseudolongum* was attributed to its metabolite inosine, which can promote the activation of Th1 cells via T cell specific $A_{2A}R$ signaling.[38] Interestingly, the sensitization of *Akkermansia muciniphila* to ICIs response can also be attributed to inosine-$A_{2A}R$ signaling.[38] ICD inducers, such as chemotherapeutic regimens, radiotherapy, and photodynamic therapy, have been reported to be associated with gut microbiota.[39–41] Cyclophosphamide (CTX), a recognized ICD inducer, was demonstrated to alter the composition of gut microbiota, enhance the "pathogenic" T helper (pTh17) cells and Th1 cells to stimulate anti-tumor immune response.[41] Collectively, manipulation of gut microbiota has been a new strategy for prevention and treatment of cancers.

Analogous to gut microbiota, fungi also can exert an impact on cancer progression and patient prognosis. Despite fungi accounts for about 0.01%–2% in our gut microbiome, emerging evidence showed the association between fungi and cancer. ITS1 sequencing of fecal samples showed that in hepatocellular carcinoma (HCC) patients exhibited decreased alpha diversity and higher abundance of the *Candida* genus and *Candida albicans* compared to liver cirrhosis patients.[42] However, in melanoma and bladder cancer patients, the fungal alpha diversity in stools was found higher compared to healthy donors.[43,44] In addition to gut microbiome, Lian Narunsky-Haziza et al. comprehensively characterized fungi communities within 17,401 biological samples (tissue, blood, and plasma) across 35 cancer types. They found that fungi are commonly present in cancer and immune cells. These intratumoral fungi were associated with clinical survival and immunotherapy response.[45] *Malassezia globose* was strongly associated with pancreatic and breast tumorigenesis.[45] *Candida tropicalis*, a fungus associated with inflammation and immune activation, has higher abundance in gastrointestinal tumors which may be a prognosis marker.[46] Mechanistically, fungi may modulate tumors through the production of metabolites, interaction of bacteria, and modulation of host immunity.[47] However, the research on fungi and cancer is still in its infancy; much work is required to reveal the interactions among fungi, bacteria, and the host.

Thirteen percent of the global cancers are associated with viral infection.[48] Yet engineered viruses or oncolytic viruses hold the potential to attack and destroy tumor cells. Talimogene laherparepvec (T-VEC) is the first FDA-approved engineered oncolytic virus for the treatment of advanced melanoma patients.[49] T-VEC as monotherapy can exhibit good performance on the improvement of survival for unresectable, stage IIIB-IVM1a melanoma patients. It can also enhance the response to ICIs in combination therapy. Oncolytic viruses mainly exert anti-tumor effect via (1) selective replication within tumor cells; (2) delivery of multiscale eukaryotic transgene payloads; (3) induction of ICD and activation of anti-tumor immunity. Oncolytic viruses have a tolerable safety, but challenges still remain need to be addressed in optimizing suitable clinical endpoints, regulatory pathways, and clinical logistics.[50]

Collectively, a growing body of evidence indicates that targeting the microbiome may hold the key to fighting cancers (Figure 1). In the latest paper "the hallmarks of cancer", polymorphic microbes have been included as a new emerging cancer hallmark.[18]

3 | IMMUNOGENIC CELL DEATH AND CANCER

The Nomenclature Committee on Cell Death (NCCD) defined immunogenic cell death (ICD) as a form of regulated cell death, which is sufficient to activate adaptive immune response to facilitate the anticancer effect.[4] ICD can initiate adaptive immune responses when exposed to DAMPs, including but not limited to the translocation

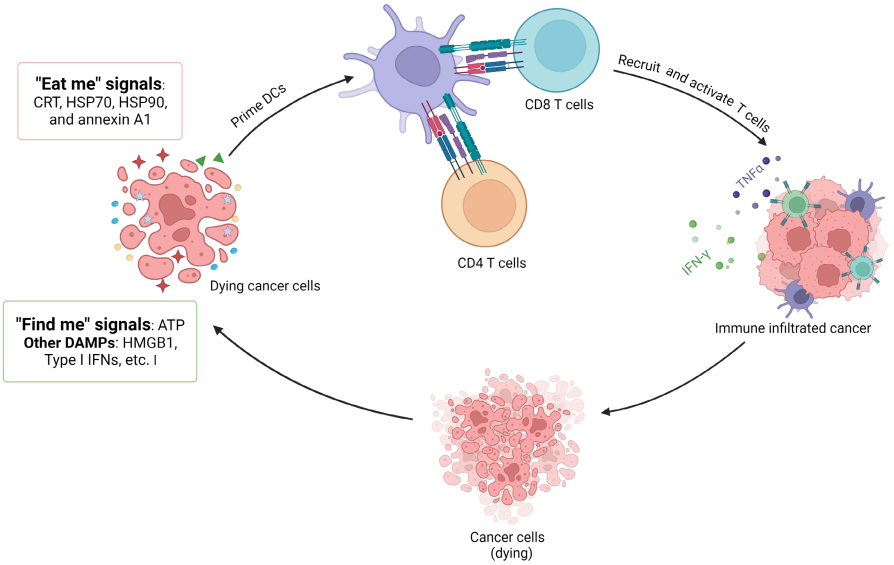

FIGURE 1 Polymorphic microbes has been considered as a new emerging cancer hallmark. Human microbiome (bacteria, virus, and fungi) plays a crucial role in the development and progression of various cancers. Beneficial microbes could inhibit tumor growth, while harmful microbes may promote the occurrence and deterioration of tumors.

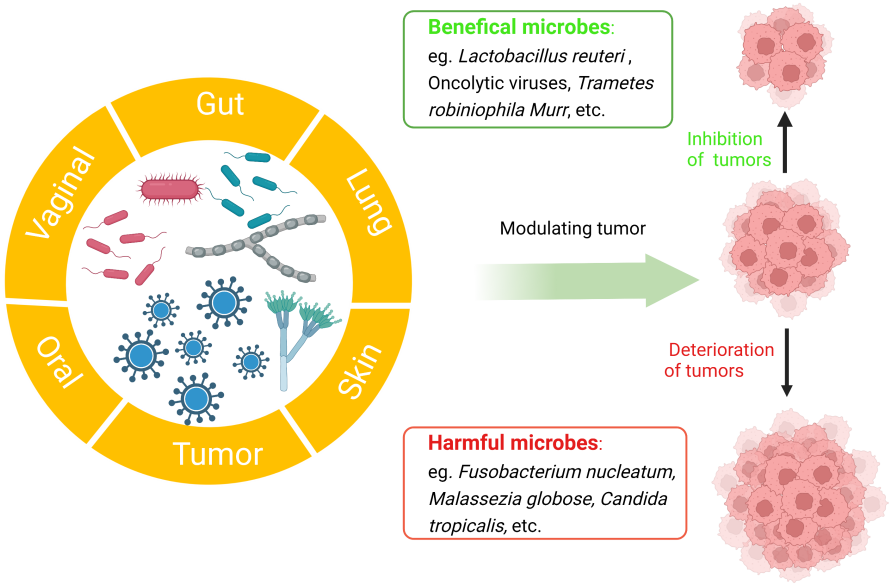

FIGURE 2 Process of ICD. Dying cells release "find me" and/or "eat me" signals to promote phagocytes to promote phagocytosis of the damaged cells, which in turn prime maturation of DCs and initiate adaptive immune response. The common "eat me" signals include CRT, HSP70, HSP90, and annexin A1. ATP represents the "find me" signal. ICD can also be induced by other DMAPs, such as HMGB1 and Type I IFNs.

of calreticulin (CRT), the release of heat shock protein (HSP) 70, HSP90, the secretion of high mobility group box 1 (HMGB1), extracellular adenosine triphosphate (ATP), and immunostimulatory cytokines, type I interferon (IFN) which are secreted or released by stressed or injured, or dying cells.[51–53] In the process of ICD, dying cells release "find me" and/or "eat me" signals to promote phagocytes to promote phagocytosis of the damaged cells, which in turn prime maturation of dendritic cells (DCs) and initiate adaptive immune response[54] (Figure 2).

3.1 | "Find-me" signals in the course of ICD

In the course of ICD, "find-me" signal is an important biological event that guides the immune system to recognize and clear the dying cells. Extracellular ATP can serve as a "find-me" signal by binding to purinergic receptors on target cells, such as purinergic receptor P2Y2 (PERY2)[55] and purinergic receptor P2X7 (P2RX7).[56] P2RX7 is an extracellular ATP-gated channel which is highly expressed in immune cells. P2RX7 signaling plays a critical role in the formation and maintenance of memory T cells and tissue-resident memory T cells.[57,58] When ATP binds to P2RX7, it will trigger the cascade signaling pathway via eliciting the influx of Ca^{2+}, leading to the maturation and activation of DCs, which can further activate T cells.[59] In addition, the binding of ATP and P2RX7 was demonstrated to trigger the activation of NOD-like receptor family, pyrin domain containing-3 protein (NLRP3) inflammasome in DCs, followed by the priming of cytotoxic $CD8^+$ T cells via the secretion of IL-1β.[56] Several chemotherapeutic regimens, such as oxaliplatin, CTX, have been shown the efficacy to induce ICD via the release of ATP. The trafficking mechanism underlying the secreted ATP depends on both apoptotic stage and the stress types or cell death stimulus. The release of ATP triggered by oxaliplatin and mitoxantrone in osteosarcoma U2OS cells is involved in the lysosomal protein LAMP1 and myosin II-dependent cellular blebbing. LAMP1 redistributes ATP from lysosomes to autolysosomes in a caspase- and pannexin 1 (PANX1)-dependent manner.[60] Additionally, in tumor microenvironment, extracellular ATP can be degraded by ecto-enzymes CD39 (ecto-nucleoside triphosphate diphosphohydrolase 1, E-NTPDase1) and CD73 (ecto-5'-nucleotidase, Ecto5NTase), which have the capability to produce adenosine and suppress anti-tumor immune response via adenosine P1 receptors. Consistent with the role of CD39, overexpression of CD39 on tumor cells was demonstrate to abolish the induction effect of ICD in vivo, thus compromising the anti-tumor effect of chemotherapeutic regimens.[61] Altogether, these mechanisms highlight the importance of the extracellular ATP in initiating and activating adaptive immunity during ICD.

3.2 | "Eat-me" signals in ICD

"Eat-me" signals are molecules exposed on the surface of dying cells which prompt the recognition and engulfment by phagocytes. The most characterized eat-me signals in ICD include CRT, HSP70, and HSP90, which mainly exposed on the plasma membrane. ICD is one of stress-associated cell death, which may lead to the generation of ROS and accumulation of misfolded proteins. CRT is a soluble chaperone protein that binds calcium involved in the regulation of Ca^{2+} homeostasis and help other protein fold correctly in endoplasmic reticulum (ER), which consists of three distinct domains, including an amino N-domain, a central or proline-rich P domain, and a highly acidic carboxyl (C)-terminal domain.[62] Under normal circumstances, CRT is situated within the ER lumen, whereas in response to ICD inducers, it will be translocated to the cell surface at an initial stage, subsequently facilitating the activation of DC mediated T-cell anti-tumor immunity.[63] The mechanisms in CRT translocation varies depending on the specific inducers involved. Anthracyclines and oxaliplatin can effectively drive the SNARE-dependent translocation of CRT by stimulating

PKR-like ER kinase (PERK)-mediated phosphorylation of eIF2α that subsequently triggers cleavage of caspase-8-mediated B-cell receptor associated protein 31 (BCAP31) and activation of BAX/BAK.[51,64] Mitoxantrone induced CRT exposure relies on ERp57 protein. ERp57 knockdown can abolish the translocation of CRT.[65] Besides the activation of adaptive immune system, the latest research found that CRT can also induce ICD by directly binding to NKp46 via P domain, thus activating the NK signaling pathway. This process has been demonstrated to exhibit the inhibition of tumor growth in B16 melanoma and KRAS mutation lung cancer mouse models.[66]

HSP70 and HSP90 play a critical role in cancer initiation and progression, which are also known to enhance the expression of "eat-me" signals, particularly HSP70. HSP70 is over-represent in most of cancer cells, such as breast cancer, colon, liver, esophagus, cervix, and prostate cancer.[67] HSPs can induce the secretion of proinflammatory cytokines, such as TNF-α, interleukin (IL)-1β, IL-12.[68–70] In the course of ICD, HSP70 and HSP90 can be translocated from ER to the cell surface during the mid-apoptosis. Subsequently, extracellular HSP70 and HSP90 interact with receptors on APCs, such as CD91, LOX1, and CD40 to prime DCs and activate $CD8^+$ T cells.[71,72] However, this DC activation can be abolished by blocking HSP70 and HSP90.[73] Besides, HMGB1 was shown to synergize with ATP to induce ICD by releasing IL-1β and this effect can be abrogated after treatment with HMGB1 antibody.[56] Taken together, these observations indicate the critical role of HMGB1 for cell death immunogenicity.

In the context of ICD, annexin A1 is also a component of "eat-me" signals, which expressed on the surface of the dying cells. When succumb to dying cells, annexin A1 can elicit ICD by binding to its ligand, formyl peptide receptor (FPR1), thereby activating anti-tumor immune response in anthracycline-based chemotherapy.[74] In summary, "eat-me" signals play an important role in both clearance of dying cells and the activation of immune system in the course of ICD.

3.3 | HMGB1

HMGB1 is a highly conserved superfamily of high mobility group protein, which is considered to be an immunostimulatory protein by binding to several PRRs on APCs, including TLR 2 and 4.[75] HMGB1 is secreted at the late stage of cell death. In the process of ICD, the release of HMGB1 undergoes a two-step translocation across the nuclear and plasma membrane at the post-apoptotic stage. In the nucleus, HMGB1 serves as a DNA chaperone to maintain the structure and function of chromosomes.[76] In the cytoplasm, HMGB1 can bind to TLR4 on immature DCs stimulating the maturation of DCs via TLR4/MyD88 pathway, thereby activating cytotoxic T cells.[75] HMGB1 can also regulate the maturation and antigen-presentation function of DCs via PI3K/Akt/mTOR signaling.[77,78] Altogether, HMGB1 plays a critical role in cancer therapy by mediating ICD.

3.4 | Other DAMPs in ICD

Type I IFNs signals will be activated upon virial or bacterial infection to induce inflammatory response through the activation of TLR3 by self-RNA emitted from dying cells or the cGAS/STING pathway in response to mtDNA release.[79] For example, lipopolysaccharide on outer wall of Gram-negative bacteria and bacterial flagellin, promotes the synthesis of type I IFNs.

Collectively, DAMPs and DAMP-related stress responses may have prognosis or predictive value in various cancers.[80–83] In addition, strong body of evidence supports that ICD can augment therapeutic efficacy of conventional cancer therapies, including chemotherapy,[36,84] radiotherapy,[85] and photodynamic nanotherapeutics.[86] Devoting efforts to comprehend and investigate the role and function of these signals will also help to deepen the knowledge and understanding of ICD and immune system pathways.

4 | CROSSTALK BETWEEN MICROBES AND ICD IN CANCER DEVELOPMENT

4.1 | Microbes exert anti-tumor effect by inducing ICD

Prior to the induction of adaptive immunity by microbes, specific MAMPs were detected to be expressed on multiple cells, including monocytes, macrophages, DCs, and other components of the innate immune system.[87] Thus, immunogenic microbes may serve as a mediator to induce ICD in cancer treatment (Table 1).

4.1.1 | Bacteria or microbial metabolites involved in ICD-related cancers

A number of bacteria and their associated metabolites were demonstrated to be capable of initiating ICD in cancer cells. CP1 a uropathogenic *Escherichia coli* can home to and colonize tumors to induce ICD of tumor cells, increase cytotoxicity of tumor-infiltrating lymphocytes, and sensitize response to immunotherapy in MYC- and PTEN-mutant prostate cancer models.[88] *Pseudomonas aeruginosa* can trigger robust and durable anti-tumor response by promoting tumor cell death with the secretion of HMGB-1, thereby stimulating DC maturation via TLR4/myD88 signaling and eliciting a long-lasting anti-tumor immunity.[89] Additionally, peptidoglycan derived from *Lactobacillus paracasei subp. paracasei X12* could induce ICD in colon cancer cell model through the release of HMGB1 and translocation of CRT.[90] Beyond the direct induction of bacteria, a new strategy was designed by loading oxaliplatin into bacterial ghosts which are empty cell envelopes from Gram-negative bacteria. Bacterial ghosts are considered as effective adjuvants to induce secretion of proinflammatory cytokines, thereby activating T- and B-cell immune response. By loading oxaliplatin into bacterial ghosts can synergize the anti-tumor efficacy by enhancing the induction

TABLE 1 Microbes related to ICD.

Microbes	Cancer type	Mechanisms	Refs
Bacteria			
Escherichia coli	MYC- and PTEN-mutant prostate cancer models	Polarization of tumor-associated macrophages by ICD to increase cytotoxicity of tumor-infiltrating lymphocytes, and sensitize response to immunotherapy	91
Pseudomonas aeruginosa	TC-1 tumor cells	Promoting tumor cell death with the secretion of HMGB-1, thereby stimulating DC maturation via TLR4/myD88 signaling and eliciting a long-lasting anti-tumor immunity	88
Lactobacillus paracasei subp. paracasei X12	HT29 colon cancer cell	Trigger ICD via the release of HMGB1 and translocation of CRT	89
Erysipelotrichaceae and *Bacteroides fragilis*	Colon cancer	Induce ICD via the activation of IL-1β-dependent T_{FH} cells in patients and mice with colon cancer, which contributes to the efficacy of oxaliplatin-induced immune response	93
Oncolytic virus			
Oncolytic adenovirus OBP-702	PAN02 syngeneic tumor model	Promote ICD by the secretion of extracellular ATP and HMGB1, contributing to augmenting the response to anti-PD-1 inhibitors in PAN02 syngeneic tumor model	97
Oncolytic peptide LTX-35	B16 melanomas; MCA205 fibrosarcomas	Induced ICD via Bax/Bak-mediated mitochondrial membrane permeabilization	98
Oncolytic Newcastle disease virus (NDV) strain FMW	Glioma, melanoma, lung cancer, prostate cell cancer	Induced ICD via secreting HSP70/90 and ATP, as well as mediating CRT exposure and HMGB1 release in various cancers in vitro and in vivo	99–102
Measles virus (MV) Edmonston strain	Hepatocellular carcinoma (HCC)	Induced ICD via the release of type I IFNs and HMGB1 in melanoma; increase CRT exposure, secretion of ATP and HMGB1 in hepatocellular carcinoma (HCC), thereby enhancing anti-tumor immunity of $CD8^+NKG2D^+$ cells	104
Fungi			
Trametes robiniophila Murr	Triple negative breast cancer (TNBC) cells	Induced ICD via circCLASP1/PKR/eIF2alpha signaling with the exposure of CRT, the enhanced release of ATP and HMGB1 in vitro.	107
Aspergillus ustus	TNBC cells	MHO7 derived from *Aspergillus ustus* triggered severe ER stress through PERK/eIF2α/AFT4/CHOP pathway and promote the release of ICD-associated DAMPs and further activated anti-tumor immunity in vivo.	108
Fusarium tricinctum	TNBC cells	Serve as a HSP90 inhibitor to induce TNBC cell ICD. It can also decrease PD-L1 expression and activate CX3CR1 pathway to mobilize $CD8^+$ T cells to tumor site to eradicate the tumor cells	109

of ICD, contributing to stronger anti-tumor effect of oxaliplatin in colorectal cancer (CRC) mouse model.[91] Similarly, a nanoparticles/bacteria complex (Ec-PR848), which is composed of toll-like receptor 7/8 agonist PLGA-R848 and *Escherichia coli* MG1655, could induce tumor-associated macrophages polarization from M2 to M1 macrophages and ICD both in vitro and in vivo in breast cancer.[92] Collectively, these results indicate that immunogenic bacteria are a potential candidate to drive ICD in cancer treatment.

Mounting evidence supports the notion that antibiotics treatments severely weaken the anti-tumor efficacy of chemotherapy, radiotherapy, and immunotherapy by disturbing the gut microbiota.[36] Manipulating gut microbiota to sensitize the responsiveness to cancer therapy has been a promising strategy. Oxaliplatin was found to have strong immunogenicity and elicit anti-tumor immune response in colon cancer. However, antibiotics (ABX)-treated and germ-free (GF) tumor-bearing mice failed to respond to oxaliplatin. Further study found this suppression of tumor regression occurred in early stage by decreasing oxaliplatin cytotoxicity and reducing myeloid-cell ROS production, results in the failure of ICD.[93] Moreover, the anti-tumor efficacy of oxaliplatin was also found to be associated with the apoptosis of ileal crypts which governed by the ileal microbiome. Immunogenic *Erysipelotrichaceae* and *Bacteroides fragilis* in the ileal determines ICD of ileal intestinal epithelial cells and the activation of IL-1β-dependent T_{FH} cells in patients and mice with colon cancer, which contributes to the efficacy of oxaliplatin-induced immune response.[94] Cyclophosphamide (CTX), an alkylated anticancer agent and ICD inducer, was also demonstrated to induce anti-tumor immunity of Th17 and Th1 cells in mouse models, which was dependent on Gram positive bacteria, such as *Lactobacillus johnsonii*, *Lactobacillus murinus*, and *Enterococcus hirae*.[41] Beyond gut microbiota, microbial metabolites also exhibit anti-tumor effect by triggering ICD pathway. Microbial vitamin B6 precursor could convert the way of death of cancer cells which succumbed to cisplatin derivatives (cis-diamminedichloroplatinum) into ICD in non-small cell lung

cancer mouse model.[95,96] Taken together, it is tempting to speculate that harness of gut microbiota is a potential intervention to induce ICD in the treatment of cancers. However, the underlying molecular mechanism needs more investigation.

4.1.2 | Oncolytic virus (OVs) involved ICD controls tumor growth

Oncolytic viruses possess the ability to selectively target and lyse cancer cells, thereby inducing ICD and provoke potent and long-lasting anti-tumor immunity. Certain OVs display natural tropism for tumor tissues, whereas others are genetically engineered to identify and replicate in cancer cells, as well as deliver specific genes. Oncolytic viruses are a novel therapeutic agents through inducing ICD for cancer immunotherapy.[97] Following oncolytic cell death, dying cancer cells can release viral PAMPs and ICD-related DAMPs, such as heat shock proteins, HMGB1, CRT, ATP, and uric acid, as well as cytokines like type I IFNs, TNFα, IFN-γ, and IL-12, which can stimulate the maturation of antigen-presenting cells (APCs), such as DCs. This, in turn, elicits anti-tumor $CD4^+$ and $CD8^+$ T-cell responses.[97] Oncolytic adenovirus OBP-702-mediated p53 overexpression significantly enhanced ICD with secretion of extracellular ATP and HMGB1, contributing to augmenting the response to anti-PD1 inhibitor in PAN02 syngeneic tumor model.[98] Oncolytic peptide LTX-35 exhibited a strong anti-tumor T-cell immunity by inducing ICD via Bax/Bak-mediated mitochondrial membrane permeabilization.[99] What's more, Oncolytic Newcastle disease virus (NDV) strain FMW has been demonstrated to be a potent inducer of ICD via secreting HSP70/90 and ATP, as well as mediating CRT exposure and HMGB1 release in various cancers in vitro and in vivo, including glioma,[100] lung cancer,[101] melanoma,[102] and prostate cell cancer.[103] Measles virus (MV) Edmonston strain induced the release of type I IFNs and HMGB1 in melanoma.[104] MV Edmonston strain can also increase CRT exposure, secretion of ATP and HMGB1 in hepatocellular carcinoma (HCC), thereby enhancing anti-tumor immunity of $CD8^+NKG2D^+$ cells.[105] In addition, extensive evidence indicates that oncolytic viruses possess the potential to serve as adjuvant for immune checkpoint therapy. In a phase 1b clinical trial, 21 advanced melanoma patients received intratumoral injection of talimogene laherparepvec (an engineered herpes simplex virus type 1) combined with anti-PD-1 inhibitors. The combination therapy exhibited a high overall response rate and complete response rate of 62% and 33%, respectively. Responders experienced a higher PD-L1 expression and more robust anti-tumor response of $CD8^+$ T cells in tumor microenvironment.[106] Altogether, the OVs can trigger ICD via expression of danger signals to enhance the anti-tumor immunity. Thus, modulating immunogenic OVs is emerging a potent strategy to enhance the anti-tumor effect in cancer immunotherapy.

Furthermore, considering nanosized drug delivery systems (NDDS) has the capacity to trigger ICD, Li et al. developed a pseudovirus platform which encapsules self-replicating IL-12 RNA into oncolytic nanoparticles to eradicate cancer cells and remodel tumor microenvironment via induction of ICD, activation of DCs, and recruitment of cytotoxic tumor-infiltrating lymphocytes to facilitate anti-tumor immunity and immune memory.[107] This strategy may provide a new insight in developing new cancer therapies by NDDS to enhance ICD of cancer cells.

4.1.3 | Fungi or its by-products enhance anti-tumor immunity by inducing ICD

Studies showed that multiple species of fungi were detected in each of the 35 cancer types in a study of 17,000 tissue and blood samples. Furthermore, each cancer type was associated with a unique combination of fungal species, which potentially have implications to affect cancer detection, diagnosis, and even treatment.[45] Moreover, fungi were also detected in fecal samples from HCC, melanoma, and bladder cancer patients by ITS sequencing.[42–44] However, how these fungi influence cancer remains unclear. Fungi-induced ICD may provide a new insight to reveal the vail.

Trametes robiniophila Murr from Chinese herbal Huaier was reported to inhibit triple negative breast cancer (TNBC) progression via inducing ICD with the exposure of CRT, the enhanced release of ATP and HMGB1 in vitro. Oral administration of Huaier to tumor-bearing mice demonstrated the enhanced cytotoxicity of tumor-infiltrating lymphocytes and delayed tumor growth. This anti-tumor effect was mainly associated with ER stress-associated ICD by promoting the exposure to CRT, release of ATP and HMGB1 in TNBC cells. Further study found that the induction of ICD was triggered through circCLASP1/PKR/eIF2α signaling pathway.[108] MHO7 (6-epi-ophiobolin G), a small molecule from *Aspergillus ustus*, elicited cytotoxic effect on TNBC cells at a low IC_{50} from 0.96 to 1.75 μM. MHO7 triggered severe ER stress through PERK/eIF2α/AFT4/CHOP pathway and promote the release of ICD-associated DAMPs and further activated anti-tumor immunity in vivo.[109] EnnA, a peptide isolated from *Fusarium tricinctum*, can serve as a HSP90 inhibitor to induce TNBC cell ICD. It can also decrease PD-L1 expression and activate CX3CR1 pathway to mobilize $CD8^+$ T cells to tumor site to eradicate the tumor cells, which hints that EnnA is a potential immune enhancer to ICIs.[110] Taken together, these findings provide a tentative validation of the concept that fungi-induced ICD contributes to the success of cancer immunotherapy.

4.2 | Targeting microbes-mediated ICD in cancer immunotherapy

Microbes-mediated ICD induction provides a robust anti-tumor immune microenvironment, making it a new option for cancer immunotherapy. CP1, an uropathogenic *Escherichia coli* (UPEC) isolated from a chronic prostatitis patient, exhibited multifaceted immunomodulatory effect in cancer treatment. It can enhance cytotoxic of T cells by increased secretion of IFN-γ, granzyme B, perforin, and TNF-α. It can also skew the balance of Th17/Treg to increase Th17 cells and

decrease Treg cells.[88,111,112] It can also induce maturation of DCs, M1 macrophages, NK cells, and γδ T cells, reduce VEGF and IL-6 in tumor tissues, and directly kill cancer cells by inducing ICD.[88] Additionally, CP1 is capable of reprograming prostate tumor microenvironment and sensitize the response to PD-1 immunotherapy by combination with anti-PD-1 blockade.[88] SS1P, an immunotoxin synthesized from *Pseudomonas exotoxin* A, has the potential to secret ATP and increase CRT expression on AE17M mouse mesothelioma cells to induce ICD. Intratumoral injection of SS1P could facilitate anti-tumor effect of CTLA-4 and prolonged survival in mesothelioma mouse model.[113] Bacterial flagellin can also serve as an ICD inducer, which is capable to elicit RIP1-mediate cell death and activate cross-presentation of DCs to enhance anti-tumor effect in immunotherapy.[114] Collectively, these examples indicate that microbe-mediated ICD has been widely studied for enhancing cancer immunotherapy.

4.3 | Traditional Chinese medicines (TCMs) related ICD in cancer therapy

TCM-derived compounds and extracts play a critical role in cancer treatment for their immunomodulation efficacy. Growing evidence supports that certain TCMs elicit anti-tumor effect by inducing ICD (Figure 3, Table 2). Ginsenoside Rg3 has been demonstrated to suppress tumor growth in various cancers, such as lung, ovarian, and melanoma. It was found that the anti-tumor effect can be associated with ICD, accompanied by the increase of HSP60, HSP70, HSP90, and translocation of CRT on LLC and B16F10 cell lines, thus activating DC-based immunotherapy.[115] Shikonin was demonstrated to be an adjuvant for DC-based cancer vaccines via inducing ICD with upregulation of HSP70 and translocation of CRT. Dying tumor cells could further promote the maturation of DCs and activate Th1 cells.[116,117] Oleandrin, a cardiac glycoside, triggered endoplasmic reticulum (ER) stress and inducing CRT exposure, and release of HMGB1, HSP70/90, and ATP in breast cancer cells. Mechanistic study showed that oleandrin induced caspase-independent ICD mainly via PERK/eIF2α/ATF4/CHOP pathway. Moreover, oleandrin potentiated anti-tumor immune response when combined with immune checkpoint inhibitors.[118] Colchicine and other two 2-phenyl-4-quinolone analogues could induce ICD in tumor cells by increasing the expression of HSP70, HSP90, and HMGB1, which can prime DCs-mediated anti-tumor immunity.[119] Wogonin elicited ER stress in a PERK/AKT dependent manner and triggered CRT/Annexin A1 translocation and release of HMGB1 in gastric cancer cells, which further mediated anti-tumor immunity.[120] Paclitaxel could activate anti-tumor immunity by inducing CRT translocation, ATP production, and HMGB1 release in ovarian cancer cells through TLR4/IKK2/SNARE exocytosis.[121] To improve the immunogenic potential of drugs, nanocarrier-mediated combinations also attract scientists' attention. Alantolactone, a sesquiterpene lactone from *Inula racemose Hook. f.*, was found to induce ICD on CT26-FL3 mouse model. Quercetin has been demonstrated to inhibit tumor growth in various cancers, such as breast, pancreatic cancers, cervical, and prostate cancers.[122–125] Quercetin can increase the generation of ROS instead of induction of ICD. Nevertheless, when quercetin combined with alantolactone at a molar ratio of 1:4, it can synergize the induction effect of ICD at a lower concentration and facilitating anti-tumor immunity.[126] Similarly, celastrol combined with mitoxantrone at a molar ratio of 1:5 could also improve ICD and elicit longer anti-tumor immunity and prolong survival.[127] Icaritin could trigger mitophagy and apoptosis of hepatocellular carcinoma (HCC) cells. When Icaritin combined with doxorubicin at a molar ratio of 1:2 elicited a robust anti-tumor immunity by inducing ICD in HCC mouse model.[128] The aforementioned examples illustrate that it is a promising approach to combine natural products with anticancer regimens as a means of triggering ICD, thereby enhancing the anti-tumor immune response.

4.4 | Clinical trials of anticancer drugs targeting ICD

According to the records in ClinicalTrials.gov database (http://www.clinicaltrials.gov/), thousands of clinical trials related to ICD are being carried out.[6] PT-112, the first pyrophosphate-platinum, possess the ability to trigger ICD and has undergone phase I clinical trials, both as a monotherapy and in combination with PD-L1 inhibitors. The phase I clinical trials of PT-112 have shown its safety in advanced solid tumors, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and thymoma. Reductions in radiological and serum markers were observed in 10 patients with metastatic castration-resistant prostate cancer. Currently, a phase II study in metastatic castrate-resistant prostate cancer (NCT02266745) is ongoing at dosage of 360 mg/m^2 as directly by the results from the completed phase I study.[110] Besides, the phase I/II clinical study on biliary tract cancer (NCT05357196), thymic epithelial tumor (NCT05104736), multiple myeloma (NCT03288480), NSCLC (NCT03409458, NCT02884479), and advanced hepatocellular carcinoma (NCT03439761) are undergoing. Moreover, oncolytic viruses, as an important ICD inducer, have also achieved results in clinical studies. In a Phase I clinical study, DNX-2401 significantly improved long-term survival in patients with recurrent high-grade glioma (NCT00805376).[129] Whether used alone or in combination with mitomycin C, CAVATAK caused a significant inflammatory response in NMIBC tissue biopsies by upregulating the IFN-inducing gene, as well as RIG-I. In addition, no significant toxic effects were reported with either the virus or the combination therapy (NCT02316171).[130] In similar studies, intratumoral administration of AdCD40L induced favorable systemic immune effects and was associated with prolonged survival (NCT01455259).[131] In addition to ICD inducers alone, the combination of multiple drugs can often enhance the effects of ICD. Over 450 clinical trials have been conducted on the combination therapy between ICD inducers and anti-PD-1/PD-L1 inhibitors according to the records in the ClinicalTrials.gov database.[132] PT-112 combined with gemcitabine for the treatment of biliary tract cancer in Phase I/II clinical trials (NCT05357196). In

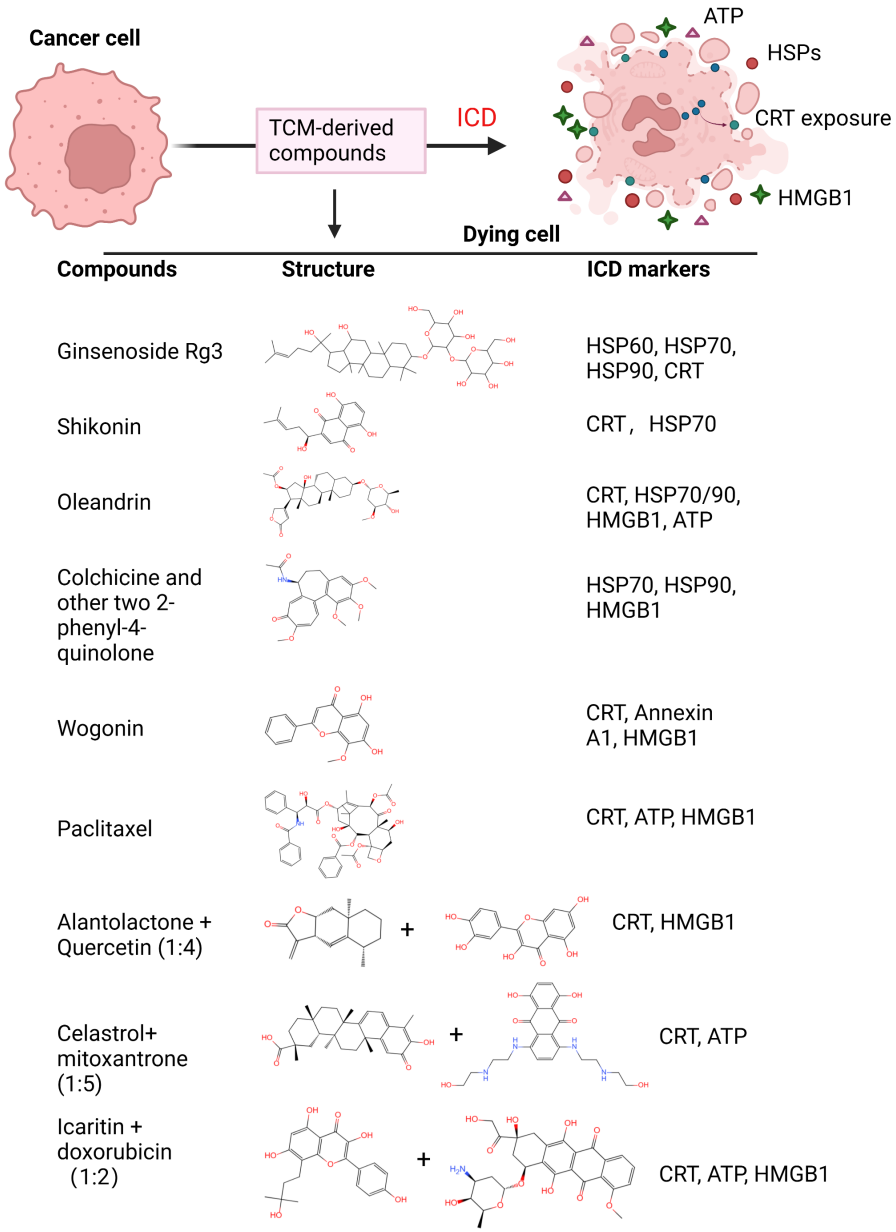

FIGURE 3 TCMs-derived compounds mediated ICD in cancer therapy. Multiple natural compounds can induce ICD alone or combined with other small molecules chemotherapeutic regimens to improve the anti-tumor efficacy.

clinical phase 1/2, PT-112 was combined with avelumab, an anti-PD-L1 antibody, for advanced solid tumors (NCT03409458). PT-112 is also used in conjunction with Docetaxel studies for advanced solid tumors and non-small cell lung cancer (NSCLC) in Phase I/II clinical trials (NCT02884479). Altogether, these clinical reports highlight the promise of ICD inducers for translational feasibility.

As a new cancer treatment strategy, microbial regulation ICD is undergoing some ongoing clinical trials, but some of them seem promising, while others fail. The following reasons may be worth discussing. First of all, it is very important that these microorganisms that induce ICD should have good tumor-specific localization. CP1 is derived from the prostate tissue of patients, and has the innate function of pro-prostate tissue, so it can be specifically located in prostate tumors without toxicity of other systems. Therefore, the anti-tumor effect of CP1 is better than that of SS1P, and CP1 has clinical application prospect. Secondly, those who can better induce the infiltration of various anti-tumor immune cells and increase the immunogenicity of tumors have more clinical prospects. Finally, whether those microorganisms can reduce the types and protein molecules of immunosuppressive immune cells in tumor microenvironment.

5 | CONCLUSIONS AND PERSPECTIVES

Currently, a significant challenge that hinders the development and advancement of ICD inducers pertains to the absence of efficient preclinical research models to mimic the intricate complexity and dynamics of tumor microenvironment. The gold standard assessment for the identification of ICD is to subcutaneously inoculated ICD inducers treated cancer cells into syngeneic immunocompetent animals and observe the ability to prevent the

TABLE 2 ICD inducers from TCM compounds.

TCM compounds	ICD markers	Cancer types	Mechanisms	Ref
Ginsenoside Rg3	HSP60, HSP70, HSP90, CRT	Lewis Lung Carcinoma cells (LLC), B16F10 melanoma cells	Rg3-induced ICD and activated DCs function.	114
Shikonin	HSP70, CRT, HMGB1	B16 melanoma cells; 4T1 breast cancer cells	HSP70 and CRT play a crucial role in Shikonin-triggered ICD for enhancement of $CD4^+$ and $CD8^+$ T-cell immunity. HSP70 has the capacity to suppress MDSC in vivo. HSP70 and HMGB1 are essential to prime DCs.	115,116
Oleandrin	CRT HMGB1, HSP70/90, and ATP	MCF7 and MDA-MB-231 breast cancer cells	Oleandrin induced ICD via PERK/eIF2α/ATF4/CHOP pathway, which subsequently enhanced $CD8^+$ T-cell immunity.	117
Colchicine, 2-phenyl-4-quinolone analogues	HSP70, HSP90, and HMGB1	B16F10 (B16) melanoma cells	Promote maturation of DCs and proliferation of $CD4^+$ and $CD8^+$ T cells	118
Wogonin	CRT, Annexin A1, HMGB1, ATP	Gastric cancer cells (MFC cells)	Wogonin activated PI3K pathway to induce ICD.	
Paclitaxel	CRT, ATP, HMGB1	Ovarian cancer cells (ID8 cells and ID8F3 cells)	Paclitaxel induced ICD through TLR4/IKK2/SNARE signal pathway.	120
Alantolactone	CRT, HMGB1	Microsatellite-Stable Colorectal Cancer (CT26-FL3)	The combination treatment of alantolactone and quercetin decreased immunosuppressive cells in the tumor microenvironment, and also promoted the systemic memory anti-tumor immunity	125
Celastrol	Hsp90, CRT, HMGB1	Murine melanoma cell lines BPD6 (BRAFV600E, PTEN−/−) and D4M (BRAFV600E, syngeneic with C57BL/6)	Celastrol synergized with mitoxantrone to indue ICD at a molar ratio of 1:5	126
Icaritin	ATP, CRT, HMGB1	Mouse Hepa1-6 and human Huh7 HCC cells	Icaritin-activated autophagy facilitated doxorubicin-induced ICD at a molar ratio of 1:2	127

cancer cell rechallenge. Besides, when cancer cells succumbed to diversified ICD inducers, how DAMPs were released from the dying cancer cells. In addition, despite the robust effects were observed in vitro and in vivo mouse models, the clinical translation may still fail. To address these issues, organ-on-a-chip models have gained much attention as a novel and promising experimental platform to investigate the interaction between tumor and immunity. This platform would benefit the elucidation of the molecular mechanisms and improve the success of translational studies of ICD inducers.[133] What's more, the combination strategy of ICD inducers and cancer regimens is a promising therapy, however, how to optimize the timing and dose of combination therapy remained to be solved.

While numerous chemotherapeutic regimens are capable of inducing ICD, a concise structure–function correlation has yet to be established to aid in the prediction of ICD-inducing agents. For instance, despite the fact that cisplatin and oxaliplatin possess a significant degree of structural similarity but cisplatin fails to induce ICD.[134,135] The same observations are applicable to the DNA alkylating agents, such as melphalan (which is inept at eliciting ICD)[136] and cyclophosphamide (which is widely recognized as an authentic ICD inducer).[137] Additional research effort should be put to investigate these underlying mechanisms.

In perspective, the modulation of chemotherapy regimens by gut microbiota highlights the tempting prospect that manipulation of the microbiome could be utilized as a potential strategy for optimizing the anti-tumor efficacy of ICD-mediated drugs (Figure 4). On the contrary, ICD may be a potential mechanism of microbes in cancer therapy. It is important to define these ICD-inducing microbes via 16S rRNA, and/or metagenomic sequencing and ITS sequencing from large cohort study and preclinical research. Subsequently, harnessing these beneficial microbes to maximize the anti-tumor efficacy. For instance, TCM extracts, or active small molecules can serve as prebiotics to enrich the abundance of beneficial gut microbiota. When TCMs are used in combination with ICD-triggering anticancer therapy, the anti-tumor immune response may be directly and indirectly potentiated. We can also employ synthetic biologic technology to genetically modify the gut bacteria, thereby augmenting the efficacy of ICD-mediated anticancer therapies to achieve precise intervention of the cancer. Improving drug delivery system such as applying exosomes to deliver functional metabolites to regulate ICD could also be a potential powerful therapeutic strategy.

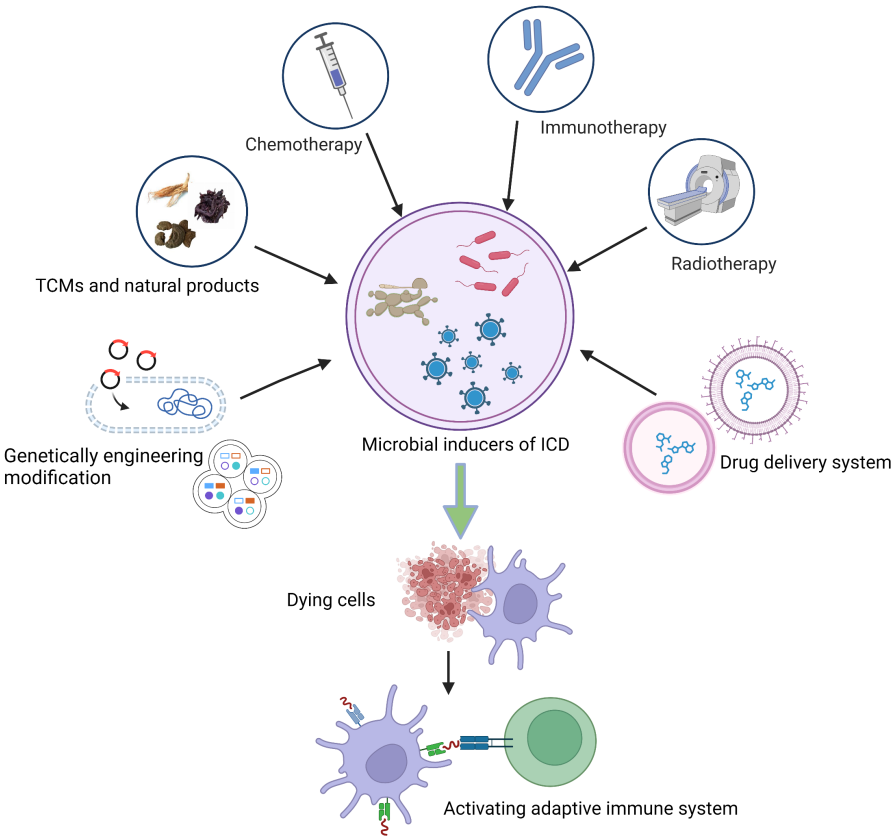

FIGURE 4 Modulatory methods of microbial inducers of ICD. Microbial inducers of ICD can be mediated or enhanced by synthetic biologic technology to genetically modified, traditional Chinese medicines (TCMs) and natural products for the enrichment, chemotherapy, immunotherapy, radiotherapy, or new combination strategy of microbial ghosts with small molecular compound.

In the future, we believed that the crosstalk in research between microbes and ICD areas will be expanding and widening the knowledges of medical and pharmaceutical sciences.

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CONFLICT OF INTEREST STATEMENT

We wish to confirm that there are no known conflicts of interest associated with this publication and that there has been no significant financial support for this work that could have influenced its outcome.

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

ORCID

Yuwei Wang https://orcid.org/0000-0001-5782-1107
Elaine Lai-Han Leung https://orcid.org/0000-0002-3705-8084

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