Japanese Journal of Gastroenterology and Hepatology

Review Article

ISSN: 2435-1210 | Volume 9

Expression Mechanism of Immunogenic Cell Death-Related Molecules in Colorectal Cancer

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Received: 28 Aug 2022
Accepted: 07 Sep 2022
Published: 12 Sep 2022
J Short Name: JJGH

Keywords:

Immunogenic cell death; Colorectal cancer; Calreticulin; Adenosine triphosphate; Heat shock protein; High mobility histone B1; Tumor immunity

Citation:

Zhang R. Expression Mechanism of Immunogenic Cell Death-Related Molecules in Colorectal Cancer. J Gstro Hepato. V9(7): 1-6

1. Abstract

Immunogenic Cell Death (ICD) plays an important role in the treatment of colorectal cancer, and the relevant molecular mechanisms of its role in colorectal cancer are closely related to a variety of Damage-Associated Molecular Patterns (DAMPs), such as calreticulin (CRT), Heat Shock Protein (HSP), Adenosine Triphosphate (ATP), high mobility group protein B1 (HMGB1) signaling molecules, Type I interferon (IFN-1) and so on. DAMPs attract natural killer cells, macrophages, dendritic cells and other innate immune cells through various pattern recognition receptors, and promote their maturation and activation to kill tumor cells and produce memory effects. ICD and its DAMPs provide a new therapeutic basis and means for the treatment of colorectal cancer. Monitoring the changes in the immunogenicity of tumor cells before and after non-surgical treatment of colorectal cancer, and organically combining chemotherapy and/or targeted therapy with immunotherapy can improve the therapeutic effect of tumors. This article reviews the expression mechanism of ICD-related molecules in colorectal cancer.

2. Introduction

With the development of the times, the technology of screening and treatment of colorectal cancer (CRC) has continued to improve. However, as the third largest malignant tumor in the world, colorectal cancer still has a high incidence, prevalence and mortality. In China, the incidence and mortality of colorectal cancer are increasing year by year, and the age of onset is even younger and younger [1-2]. For patients diagnosed with stage IV colorectal cancer, since there is currently no effective treatment option, most patients can only receive chemotherapy (eg, 5-fluorouracil, oxaliplatin, or irinotecan) and/or targeted therapy (eg, bevacizumab, targeting vascular endothelial growth factor, or cetuximab, targeting epidermal growth factor receptor), and the 5-year survival rate of patients is less than 10% [3]. The occurrence and development of colorectal cancer is very complex, including changes in the tumor microenvironment (TME), cell death, chronic inflammation, and oxidative stress. xisting studies have confirmed [4] that the immune system plays a key role in the occurrence, development and treatment of tumors. For example, changes in the tumor microenvironment can lead to immunosuppression and loss of immune surveillance to promote tumor development. Immunotherapy is bound to become a promising method to treat colorectal cancer and inhibit the recurrence and metastasis of colorectal cancer. As an important mechanism of tumor immunotherapy, immunogenic cell death (ICD) can be induced by a variety of chemical agents, radiation and targeted drugs, releasing a variety of damage-associated molecular patterns (DAMPs). ICD and its DAMPs can destroy the immunosuppressive TME and re-establish the immune surveillance of the body's tumor cells [5], thereby exerting anti-tumor effects through systemic anti-tumor immunity [6]. How to combine various anti-tumor therapies to improve clinical efficacy is an important direction in the treatment of colorectal cancer. This article reviews the expression mechanism of tumor ICD-related molecules and the regulation of immunity, and further explores the strategy of combining immunotherapy with ICD-inducing drugs, hoping to provide a theoretical basis for clinical work.

3. Immunogenic Cell Death

ICD was originally introduced by Casares et al. [7] in 2005 to describe adriamycin-challenged colorectal cancer cells (CT26) in mice, making them immunogenic. It inhibits the growth of subsequently inoculated CT26 live cells with long-term immune function. Conceptually, it is different from the programmed death of cancer cells such as autophagy, apoptosis and pyroptosis. Immunogenic cell death refers to a form of cell death in which non-immunogenic cells can transform immunogenic cells and release damage-related molecular pattern DAMPs when the body undergoes apoptosis, and finally stimulates tumor immune effects in the body [8]. ICD can function as a tumor vaccine, killing not only cells induced by ICD inducers but also dying tumor cells, thereby eliciting tumor-specific immune responses against live tumor cells and residual tumor tissue. In this way, patients can experience long-term clinical benefit from cytotoxic chemotherapy and physical induction of therapeutic responses [9]. During ICD, dying tumor cells exhibit high surface expression of damage-associated molecular patterns (DAMPs), including CRT, HSP, ATP, HMGB1 signaling molecule, IFN-1 and so on [10-12]. DAMPs attract natural killer cells, macrophages, dendritic cells and other innate immune cells through various pattern recognition receptors, and promote their maturation and activation. This completes multiple steps including clearance of dead cells, optimal antigen uptake, processing and presentation, and cytokine production, ultimately killing tumor cells within days [5]. Furthermore, mature dendritic cells trigger crossover of CD8+ cells with cytotoxic T lymphocytes (CTLs) in an IL-1β- and IL-17-dependent manner. Then CTLs trigger a direct cytotoxic response to kill tumor cells by producing IFN-γ, perforin-1 and granzyme B, while producing memory effects [5].

4. Calreticulin (CRT)

The central event in ICD is that endoplasmic reticulum (ER) stress leads to the translocation of CRT, a 46-kDa, Ca2+-binding endoplasmic reticulum chaperone, to the surface of the plasma membrane. ER stress is characterized by the phosphorylation of eukaryotic initiation factor 2α (eIF-α) by PKR-like ER kinase (PERK) in response to unfolded proteins [13]. Before ER stress-related apoptosis, ICD transfers CRT from the perinuclear endoplasmic reticulum (ER) to the cell periphery, mediated by exocytosis and the protein complex SNAP receptor (SNARE), and then relocalizes ERp57 [14-15]. When the CRT/ERp57 complex is exposed on the cell surface, it provides an "eat me" signal to stimulate the maturation of antigen-presenting cells (APCs) and bind to surface receptors for phagocytosis [16]. Surface-exposed CRT binds to low-density lipoprotein receptor-related protein-1 (LRP1, best known as CD91). LRP1 is a major chaperone-sensing pattern recognition receptor (PRR) expressed by antigen-presenting cells including DCs and macrophages [17]. Binding of CRT to CD91 triggers a series of events such as promotion of recruitment of antigen-presenting cells (eg DCs), optimal antigen presentation, release of pro-inflammatory cytokines (eg TNF-α and IL-6) and activation of type 17 helper T cells (Th17) [18]. In addition, CRT exposure to the surface of cancer cells killed by ICD also induces tumor antigen presentation and tumor-specific CTL responses [19], enhancing specific antitumor effects. Kim et al [20] confirmed that increasing the expression of CRT in colon cancer tumor cells can enhance the ability of DCs to recognize and present tumor cells and increase the number of tumor-specific CTLs. Conversely, Tatsuno et al. [21] found that knockdown of CTLs by RNA interference (RNAi), deletion by CRISPR/Cas9 or blocking CTLs by neutralizing antibodies reduced the efficacy of ICD-mediated antitumor immune responses. CRT-unexposed colon cancer cells could escape the recognition and phagocytosis of Dc after cetuximab treatment [22].

5. High Mobility Group Protein B1 (HMGB1)

HMGB1 is a non-histone chromatin-binding protein whose release from dying cells triggers a strong inflammatory response. At the end of apoptosis, when cells are damaged and destroyed, HMGB1 is released from the nucleus and gradually accumulates outside the cell, which can be detected by enzyme-linked immunosorbent assay (ELISA) [23]. Extracellular HMGB1 can bind to multiple PRRs expressed by bone marrow-derived cells, such as receptor specific for advanced glycation end products (AGER, best known as RAGE) and Toll-like receptor 4 (TLR4) [24], to activate MAPK as well as NF-ϰB in DCs. It has been reported that the binding of HMGB1 to TLR4 after release from dying cells can activate DCs and promote antigen presentation by DCs to T cells. Furthermore, recognition of HMGB1 by TLR4 subsequently triggers MyD88 (primary myeloid differentiation response gene), an adaptor for TLR4. The TLR4/MyD88 pathway enhances tumor antigen processing by inhibiting fusion between phagosomes and lysosomes, thereby accelerating the phagocytosis of antigen components by DCs and promoting the processing of phagosomes in DC [7, 25]. Nayagom et al. [26] found that knocking out HMGB1 in tumor cells or neutralizing HMGB1 antibodies would limit the immunogenic-related responses driven by anthracyclines, cyclophosphamide, and oxaliplatin in the body to produce specific anti-tumor effects. It is not difficult to see that HMGB1-mediated activation of TLR4 is a key component of ICD-induced immunogenicity. NIR-PIT-induced injury results in an influx of extracellular fluid into cells, resulting in marked rapid cell swelling. After NIR-PIT treatment of tumor cells, rapid secretion of HMGB1 could be detected. In addition, NIR-PIT-induced ICD could promote the maturation of immature dendritic cells, which contributed to the realization of durable anti-tumor immunity [27]. In vitro NIR-PIT caused mouse colorectal tumor cell death in a laser intensity dose-dependent manner. In an orthotopic colon cancer model, control mice developed persistent tumor growth, whereas mice that continued to receive NIR-PIT treatment exhibited persistent tumor growth inhibition [28].

6. Adenine Triphosphate (ATP)

Another hallmark of ICD is the secretion of ATP by dying tumor

cells during the blebbing phase of apoptosis. Autophagy is required for the secretion of ATP by dying tumor cells, and is considered to be a pre-mortem stress-adaptive mechanism that degrades cytoplasmic proteins, aggregates, and damaged organelles through catabolic processes. During its degradation, the autophagy-lysosome-lysosome complex and fusion of the lysosome and plasma membrane [29] finally allow ATP to actively exocytose ATP-containing vesicles into the extracellular space through ubiquitin channels [30-31]. Binding of extracellular ATP to the purinergic receptor P2Y2 (P2RY2, a metabotropic receptor) acts as a prominent "find-me" signal for DC precursors and macrophages [32], thereby promoting DC maturation and macrophage expansion [33]. In addition, extracellular ATP mediates pro-inflammatory effects after activating the CASP1-dependent NLRP3 inflammasome, which secretes mature interleukin 1β (IL1B, most notably IL-1β) and IL-18 [34]. These actions originate from the purinergic receptor P2X7 (P2RX7, an inotropic receptor), which ultimately activates CD8+ T cells and IL-17-producing γδ T cells [35]. Through this pathway, important cytokines are provided in the context of antigen presentation, which is also required for antigen presentation. Adaptive immune responses against cancer cells mediated by the polarization of interferon-γ (IFNγ)-producing CD8+ T cells [36]. The immunogenicity of cell death is abolished when ATP fails to accumulate in the microenvironment of dying tumor cells or when P2RX7 or P2RY2 are absent in the host's myeloid compartment [35]. Increased ATP hydrolysis by extranucleotidase enzymes such as CD39 and CD73 in the tumor microenvironment (TME) reduces tumor-infiltrating lymphocytes and weaker tumor response to chemotherapy [37]. Core-shell gold nanocages coated with manganese dioxide and hyaluronic acid (AMH) for targeted delivery to colorectal tumors for acute oxygenation-enhanced in situ immunogenic phototherapy. AMH nanoparticles can generate abundant oxygen in weakly acidic/H2O2 media, which can further enhance the oxygen-enhanced photodynamic therapy efficacy of AMH itself. Meanwhile, AMH-based oxygen-enhanced photodynamic therapy successfully enhanced ICD by inducing cellular ATP secretion. Induced ICD promotes dendritic cell maturation to further enhance systemic antitumor immunity against advanced tumors, while adequate oxygen production alleviates immunosuppression in the TME, further promoting CD8+ T cell infiltration into colorectal tumors[38,39]. CT26 cells were silenced by miRNA technology or neutralized by HMGB1 antibody, and then treated with anthracyclines, resulting in the loss of immunogenicity of tumor cells and inhibition of lymphocyte-specific anti-tumor effects. It is suggested that HMGB1 plays an important role in DC-mediated T cell activation and immunity [40].

7. Heat Shock Protein (HSP)

HSP is a highly conserved molecular chaperone, and as one of the characteristics of ICD, the expression of HSP70 and HSP90 on the membrane of dying tumor cells has immunostimulatory properties. HSP70 and HSP90 activate CTL cells and Th cells by driving the cross-presentation of tumor-derived antigenic peptides on major histocompatibility complex (MHC) class I, leading to specific CD8+ T cell responses [41, 42]. Compared with free antigenic peptides, HSP has stronger binding ability to MHC1 molecules. The combination of HSP-peptide complexes with CD14, TLR2 and TLR4 on DCs can up-regulate the expression of CD86 and CD40 in the body, which not only promotes the maturation of DCs [42,43], but also enhances their functions. It has been reported that HSP70 can promote DCs to secrete a variety of pro-inflammatory factors, such as IL-1B, IL-6, IL-8, etc., and further enhance the body's immune response [38]. The increased number of HSPs on the surface of colorectal tumor cells enhances the immunogenicity of tumor cells and promotes antitumor immune responses. In a study on HT-29 colon cell adenocarcinoma, the MTT assay found that when hypericin was combined with PDT therapy, the number of apoptotic HT-29 or HCT-116 colorectal cancer cells was significantly increased [44]. Hypericin combined with photodynamic therapy has been shown to induce phox-ER stress, leading to early induction of ecto-CRT expression, active secretion of ATP, and passive release of heat shock proteins (HSPs), such as HSP70 and HSP90. At the late stage of apoptosis, tumor development was effectively prevented by inducing ICD in naive mice [45].

8. Type I Interferon (IFN-1)

ICD is accompanied by a strong IFN-1 (α and β) response, and almost all cells can activate nucleic acid sensors after being infected by viruses or bacteria [46]. Nucleic acid sensors include RNA sensors, such as TLR3, TLR7, TLR9, RIG1/MDA5 MAVs (retinoic acid-inducible gene 1 protein/melanoma differentiation-related protein 5 mitochondrial antiviral signaling protein) [47], and DNA-containing sensors, a common one being cGAS-STING (cyclic GMP-AMP synthase-interferon gene stimulator) [48], which secretes IFN1. IFN-1 mediates significant immunostimulatory effects upon binding to homodimeric or heterodimeric receptors expressed by various immune cells [49, 50]. IFN-1 is known to enhance the cytotoxic function of CD8+ T cells and NK cells [51] and promote cross-priming of DCs [52]. Binding of IFN-1 (alpha and beta) to the IFNAR1-IFNAR2 heterodimer activates JAK/STAT signaling to establish an antiviral state that inhibits virus production, activates antigen presentation, and innate immunity to kill and clear infected cells , and ultimately improves adaptive immunity to future infections [53, 54]. In addition, IFN-1 responses regulate the highly cell-type-specific expression of numerous interferon-stimulated genes (ISGs). The IFN-1 response controls the production and function of many chemokines, cytokines and immune cells through crosstalk with the TNF-α/NF-ϰB and IL-18/IL-1β pathways. For example, IFN-1 can trigger macrophages to secrete pro-inflammatory mediators [55]; inhibit the immunosuppressive function of CD4+, CD25+, FOXP3+ regulatory T cells [56].The immunogenicity of ICDs driven by anthracyclines and radiation therapy is strongly dependent on IFN-1 signaling. When key components of the IF-1 response (such as Ifnar1,

Ifnar2, Tlr3, Cgas, or Sting1) are absent, or when IFNAR1-blocking antibodies are added to the treatment, anthracyclines and radiation therapy are significantly less effective in tumor-bearing mice [57, 58]. Thus, the dependence of type I IFN responses on the control of infection and tumor growth by host and immune cells is well established [59]. Yang et al. [60]demonstrated the role of IFN-α in regulating the EGF pathway in CRC, and treatment with IFN-α increased the expression of EGFR on the cell surface and endocytic vesicles, which significantly inhibited the growth of colorectal tumor cells . While IFN-α is involved in regulating angiogenesis in CRC, systemic administration of IFN-α inhibits colorectal cancer liver metastases and inhibits tumor growth, angiogenesis, and bFGF and MMP9 expression[60]. Recently, it has been reported that the combination therapy of IFN-α with methyltransferase and histone deacetylase inhibitors may have very promising therapeutic potential in colorectal cancer. IFN-α induces antiproliferative and proapoptotic effects on metastatic colorectal CSCs (CR-CSCs) [61]. This combined regimen was also able to induce the release of HMGB1 from CR-CSCs, thereby inducing ICD [62]. IFN-β can make CRC cells more sensitive to 5-FU treatment and has a potent effect on reducing tumor mass, suggesting a new strategy to selectively target CRC [63]. In addition to this, studies have shown that pegylated IFN-β has antitumor activity in colon xenograft models. And the combined use of pegylated IFN-β and bevacizumab was associated with greater tumor growth inhibition than pegylated IFN-β alone [64].

9. Conclusion

Further clarification of the molecular expression mechanism of colorectal cancer ICD will help to develop new drugs and provide more theoretical basis for new combination regimens. To explore the correlation of ICD-related molecules CRT, ATP, HSP, HMGB1 and IFN-1 with the immune function of the body, and to analyze the changes in tissues can predict the prognosis and survival rate of patients [65]. The dynamic changes of immune function and DAMPs in the microenvironment can improve the immune recognition ability in the tumor microenvironment. The changes of chemotherapy-related DAMPs and their use as immunotherapy synergists are very important to enhance the therapeutic effect and prolong the survival time of tumor patients. More and more studies have proved that drugs and physical methods induce ICD and trigger the body's anti-tumor immunity is an effective way to treat colorectal tumors, but more relevant clinical experiments need to be further improved. In future colorectal cancer treatment research, activation of ICD occurrence may serve as a new strategy to bring more opportunities for colorectal cancer patients to cure.

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