Review Article

Modern transformation of ancient healing arts: traditional Chinese medicine in cancer immunotherapy

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Abstract: Tumor heterogeneity remains a major challenge in the design and development of effective cancer therapy. As cells age, various mutations accumulate to alter their metabolic and survival signals. Under normal conditions, most of these cells would undergo senescence and apoptosis to maintain cellular homeostasis. However, cancer cells are unique due to their ability to escape normal cellular senescence mechanisms, leading to immortalization and uncontrolled proliferation. Recent discoveries in tumor biology have decoded many signaling pathways regulating oncogenesis, and novel therapeutic strategies have been proposed to modulate the interaction between cancer cells and host immune response, which constitutes grounds for cancer immunotherapy. The emergence of immune checkpoint blockades (ICBs) led to improved overall survival in several difficult-to-treat cancers. From the anti-CTLA4 to anti-PD-1/PD-L1 antibodies, advances in immunotherapy research and development have given patients new hope in their fights against cancer. While cancer immunotherapy agents have shown promising clinical responses in certain malignancies, tumor immune evasion remains a major obstacle in unleashing their therapeutic potential. In this review, we discuss the loss of antigenicity as a primary immune escape mechanism, elucidate current efforts for enhancing tumor antigenicity, and review the potential of traditional Chinese medicine (TCM) as a neoadjuvant or combinatorial therapy with ICBs.

Keywords: Tumor immune evasion; antigen presentation; cancer immunotherapy; traditional Chinese medicine (TCM)

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Introduction

The immune system, under normal circumstances, maintains a delicate equilibrium between the Yin and Yang of immune tolerance and autoimmunity (1). Insults at the cellular, genetic, and epigenetic levels tend to induce the tissue's physiological responses, including cell proliferation, migration, and inflammation, and facilitate either tissue repair or scarring (2-6). One of the key events leading to tumorigenesis is the disruption of immune homeostasis, in which abnormal cells accumulates mutations and epimutations (or epigenetic alterations) to evade immune surveillance, leading to uncontrolled proliferation and

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immortalization of abnormal cells (7,8).

The intricate network of immune cells orchestrates a series of mechanisms to protect the host from pathogens and diseases, and these mechanisms are dichotomized into two lines of defense: innate immunity provides immediate but nonspecific responses against threats before the more specific adaptive immune response is initiated (9). Natural killer (NK) cells and $CD8^+$ T-cells (cytotoxic T lymphocytes, CTLs) are the most potent antitumor power to recognize and eliminate cancers. NK cells of innate immunity are responsible for cancer immunosurveillance without prior sensitization (10). Major histocompatibility complex class I (MHC-I) downregulation is a significant mechanism exploited by many types of solid tumors to evade immune detection by the adaptive immune system (11-13). NK cells specifically recognize a reduction in surface MHC-I presentation, determining those cells as abnormal and eventually sending them for destruction (14). In addition to NK cells from innate immunity, CTLs from adaptive immunity also have the capacity to kill tumor cells directly. CTLs scrutinize all nucleated cells in the body via the interaction between T-cell receptors (TCRs) and antigen peptide/MHC-I complexes. CTLs induce apoptosis upon the recognition of peptides presented by MHC-I molecules on target cells (15).

During the past decades, immunotherapy has revolutionized cancer treatments and established the theoretical grounds to develop more effective treatments (16). Despite these promising discoveries, tumor cells are intelligent in developing resistance by manipulating their microenvironment and inducing anti-tumor immune cells anergy, rendering immune checkpoint blockades (ICBs) ineffective in many types of cancer (17). In this review, we briefly discuss $CD8^+$ T-cell biology and tumor immune evasion mechanisms, assess the significance of antigenicity loss in solid tumors and list ongoing efforts in enhancing antigenicity in solid tumors. We further propose several future research directions on the immunoregulatory effects of traditional Chinese medicine (TCM) as potential novel therapeutic strategies.

T cell activation and killing mechanisms

Naïve $CD8^+$ T-cells develop and mature in the thymus. These naïve cells enter the bloodstream upon maturation and circulate through the secondary lymphoid organs (15,18). They can encounter potential antigens presented by the MHC-I on antigen-presenting cells (APCs) such as dendritic cells (DCs), macrophages, and B cells (19). T-cell activation requires at least three signals: an initial antigen-specific signal, a co-stimulatory signal, and cytokines (20,21). All events must occur sequentially to induce adequate T-cell activation and response. First, the TCR of a naïve $CD8^+$ T-cell recognizes an antigen presented on the MHC-I of an APC. A CD8 co-receptor then stabilizes the initial interaction between TCR and MHC-I. After forming a stabilized complex, the expression of B7.1 or B7.2 by APCs is induced, allowing the critical second B7-CD28 co-stimulatory signal to fine-tune the T-cell response. Lastly, IL-2 production by the activated $CD8^+$ T-cells, or more often, with the help of $CD4^+$ effector T-cells, promotes differentiation into CTLs that directly kill foreign or cancer cells (22).

The duration of antigen exposure is critical to maintain effective CTLs. Antigens need to be present and recognized to trigger $CD8^+$ T-cell differentiation. The host must be able to rapidly eliminate such antigens from the system after the maturation of CTL to allow the development of memory $CD8^+$ T-cells. Memory $CD8^+$ T-cells are powerful in fighting off foreign substances upon re-exposure. In cancer and chronic viral infections, when antigens are not removed from the host promptly, neoantigens are sampled and circulated constantly. This prolonged exposure to antigens leads to desensitization and impaired memory $CD8^+$ T-cell development, resulting in $CD8^+$ T-cell exhaustion (23-29). The key features of exhausted CTLs are loss of effector functions, sustained expression of inhibitory receptors, altered transcriptional and epigenetic modifications, and metabolic reprogramming (*Figure 1*) (23). Thus, to restore CTLs activity and functions, therapeutic strategies must be considered to tackle such complex tasks at hand.

CTLs have been a primary focus in immunotherapy research due to their specificity and high efficacy in targeting tumor cells that carry specific antigens (29-33). Antigen-MHC-I complex recognition by TCR triggers the release of two populations of cytotoxic granules, inducing caspase 3-mediated apoptosis through two distinct mechanisms (34). One granule population of CTLs contains granzymes, perforins, and granulysins. The released perforins create pores on the target cell membrane, thereby delivering granzymes that activate caspase 3 intracellularly, leading to target cell apoptosis. The other granule population of CTLs consists of Fas ligands (FasLs), which activate caspase 3 by engaging the Fas receptors on the targeted cell surface. The FasL/Fas receptor interaction results in caspase 8 activation.

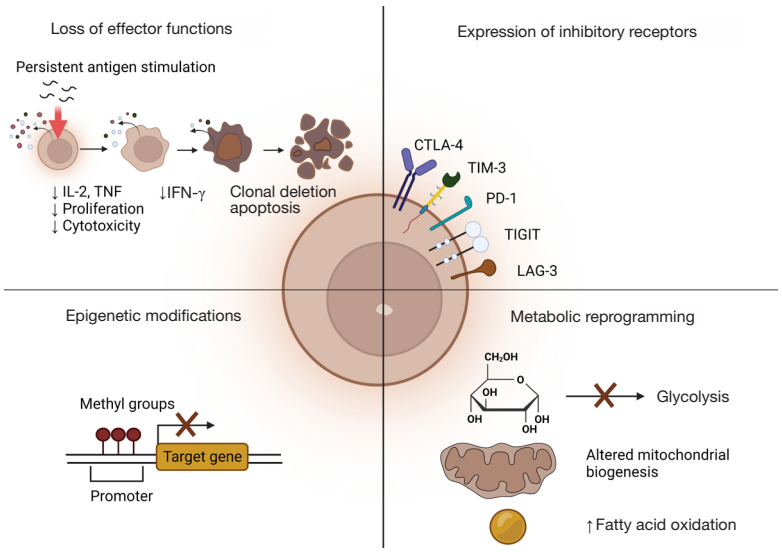

Figure 1 Key features of exhausted CTLs during prolonged antigen exposure. CTL exhaustion is characterized by the loss of effector functions. This loss of effector functions is accompanied by an early decrease in IL-2 and TNF cytokines, which leads to poor CTL proliferation and cytotoxicity. Depletion of IFN-γ at later stages eventually leads to clonal deletion and CTL apoptosis. Other exhaustion features include the expression of inhibitory receptors such as CTLA-4, TIM-3, PD-1, TIGIT, and LAG-3, epigenetic modifications such as DNA methylation of CpG sites at promoter regions, and metabolic reprogramming that alters nutrient distribution in the TME (23). Created with BioRender.com. CTL, cytotoxic T lymphocyte; TNF, tumor necrosis factor; IFN-γ, interferon-γ; CTLA-4, cytotoxic T-lymphocyte associated protein 4; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; PD-1, programmed cell death protein 1; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain; LAG-3, lymphocyte-activation gene 3; TME, tumor microenvironment.

Activated caspase 8, in turn, activates caspase 3, inducing apoptosis. TCR binding also modulates cytotoxic molecule replenishment via *de novo* synthesis, allowing a CTL to kill a series of targets in succession (35). Besides their direct killing capacity, CTLs release several cytokines, including IFN-γ, TNF-α, and TNF-β, which facilitate tumor cell recognition and elimination (36). Most importantly, IFN-γ has gained much attention in immunotherapy development due to its ability to enhance MHC-I expression and antigen loading in tumor cells (37-39).

Tumor immune evasion mechanisms overview

Cancer immunotherapy is designed to augment the immune response against tumor cells. Strategies such as ICBs and adoptive T-cell therapy have revolutionized cancer treatment (16,40,41). While ICBs have shown extensive clinical success in treating melanoma and non-small cell lung carcinomas, their effectiveness in treating many other solid tumors is limited (42-49). Tumor immune evasion through immunoediting and tumor heterogeneity are two mechanisms that are responsible for the observed suboptimal response to ICBs in many patients (50).

Tumor immune evasion poses a significant barrier to treating solid tumors. Most solid tumors employ three main mechanisms to escape immunosurveillance: loss of antigenicity, loss of immunogenicity, and suppressive tumor microenvironment (TME) (51). Sufficient antigenicity is necessary to trigger the initial immune activation. Tumor cells express a diverse population of non-mutated, tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs). TSAs are non-self-antigens only expressed by tumor cells. In contrast, TAAs are self-antigens found in normal cells but upregulated in tumor cells. Ideally, the immune system recognizes these antigens expressed by tumor cells, leading to a potent tumor-specific immune response (52-54). Usually, by selective pressures, tumor cells deprived of TSAs could circumvent immune-mediated attacks to survive and proliferate. There are several proposed mechanisms through which antigenicity could be lost. Immune cells are known to selectively eliminate tumor cells with high tumor mutation burden (TMB), allowing low TMB-tumor

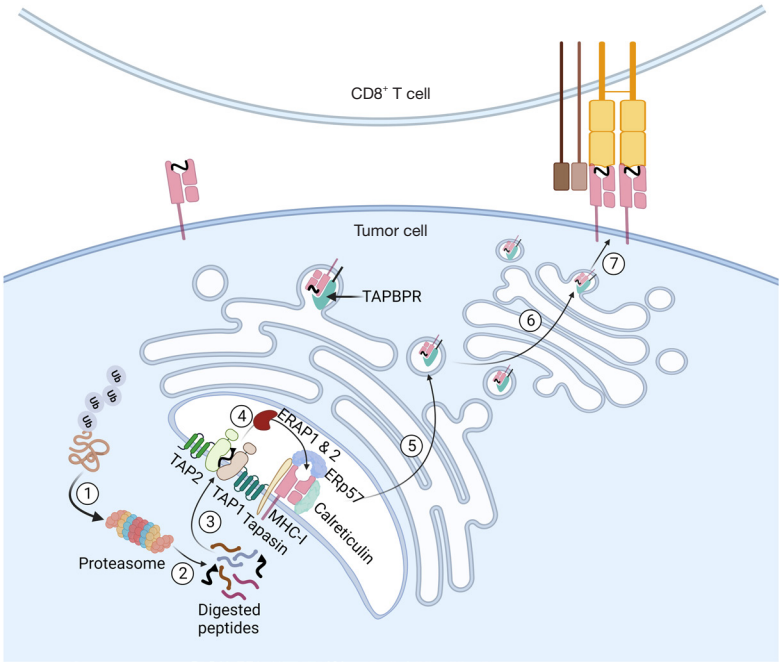

Figure 2 Antigen processing and presentation pathway. Ubiquitinated polypeptides are targeted for proteolytic processing by 26S proteasomes or immunoproteasomes (not shown in the figure) into digested peptides (①-②). Digested peptides are transported into the endoplasmic reticulum via TAP1 & 2 complex (③). Digested peptides are further processed by ERAP1 & 2 and loaded onto MHC-I with the help of tapasin, calreticulin and ERp57 (④). Peptide:MHC-I complexes are packaged into vesicles, where the complexes are stabilized by chaperones, TAPBPR, traveling through the Golgi apparatus (⑤-⑥). Finally, the vesicles fuse with the plasma membrane, allowing the peptide:MHC-I to be presented on the target cell surface for the recognition by TCRs (⑦) (57). Created with BioRender.com. TAP1 & 2, transporter associated with antigen processing 1 & 2; ERAP1 & 2, endoplasmic reticulum aminopeptidase 1 & 2; MHC-I, major histocompatibility complex class I; TAPBPR, Tapasin and TAP-binding protein related; TCR, T-cell receptor.

cell populations to replicate and thrive (51). Secondly, transformed cells acquire genetic mutations, resulting in MHC-I molecule downregulation and antigen-processing machinery dysfunction, thereby rendering antigen presentation defective in tumor cells (55,56) (*Figure 2*). In comparison, tumor cells with retained antigenicity may upregulate the inhibitory molecule expression or mask their antigenicity by producing suboptimal neoantigens. Lastly, cancer cells manipulate their TME to make it less favorable for the activation and survival of antitumor immune cells. Loss of immunogenicity and suppressive TME are two complex topics beyond the scope of this review. These two immune evasion mechanisms were discussed in detail in Beatty and Gladney's review (51).

Current efforts in targeting solid tumor antigen presentation

A potential target from the antigen processing and presentation pathway is immunoproteasome. The immunoproteasome was first described in the early 1990s, under the notion that IFN-γ induced changes in the proteasome catalytic subunits, which led to altered catalytic activity (58-62). Furthermore, peptides produced by immunoproteasomes are restricted to the MHC-I antigen processing pathway, which sets it apart from the consecutive proteasome (59,63,64). Due to its specificity only induced by IFN-γ in altered cells, conceptually, immunoproteasome is an optimal drug target for cancer immunotherapy. By selectively targeting the immunoproteasome, the immunopeptidome landscape will show MHC-I preferences, triggering more robust CTL activation and targeted killing. Immunoproteasome deficiency is associated with poor prognosis in various cancer types (65,66). Despite its ostensible advantage, current drugs targeting immunoproteasomes have shown only modest therapeutic efficacy due to the heterogeneous expression of the immunoproteasome in different tumors (67,68). Current

Table 1 Major targets in antigen processing and presentation pathway and their respective therapeutic approaches (69)

Antigen presentation pathway target	Tumor evasion mechanism	Therapeutic approaches	References
Immunoproteasome	Diminished immunopeptidome landscape	LMP7/β5i/PSMB8 inhibitors—ONX-912, PR-924, UK-101, IPSI-001	(37,70-73)
		Regulatory subunit stabilizer—ATT-I	
TAP	Reduced antigen: MHC-I complex expression	Increase T cell epitopes associated with impaired peptide processing (TEIPPs)	(74-77)
		Inhibit TAP with a siRNA vaccine	
TAPBPR	Decreased immunopeptidome repertoire	Introduction of plasma membrane targeted or exogenous soluble TAPBPR	(78-81)
ERAP1 & 2	Altered immunopeptidome	ERAP1 & 2 inhibitors	(82-94)

LMP7, large multifunctional peptidase 7; PSMB8, proteasome subunit β type 8; ATT-I, atractylenolide-I; TAP, transporter associated with antigen processing; MHC-I, major histocompatibility complex-I; TAPBPR, Tapasin and TAP-binding protein related; ERAP1 & 2, endoplasmic reticulum aminopeptidase 1 & 2.

research efforts on targeting immunotherapy are listed in *Table 1*, and other explored targets along the antigen processing and presentation pathway.

Therapeutic interventions focused on upregulating tumor antigen presentation in the breast cancer immunotherapy arena have been proposed and investigated. An epigenetic HDAC inhibitor, BML-210, has been studied previously as an effective drug to upregulate MHC-I antigen processing and presentation in triple-negative breast cancer models (TNBC) (95). This study also confirmed the effectiveness of BML-210 and PD-1 mAb as a combination therapy, thus proving that enhanced tumor MHC-I antigen presentation is a rational and effective strategy for designing improved immunotherapeutic. In another study, our laboratory identified MAL2 (Mal, T cell differentiation protein 2) as a crucial player in the recycling of antigen-loaded MHC-I complex in breast cancer models, suggesting MAL2 as a potential novel target for immunotherapy (96). Moreover, a group discovered a long noncoding RNA (lncRNA) LINK-A expression in patients with TNBC. This lncRNA was found to enhance K48-polyubiquitin-mediated degradation of the antigen peptide-load complex, which provided a new foundation for developing combinational immunotherapy treatments (97).

Enhancing antigen presentation to improve immunotherapy has been explored in other cancer types. EZH2 (Enhancer of Zeste 2 polycomb repressive complex 2) was identified as a therapeutic target that enhanced tumor cell antigen presentation in head and neck squamous cell carcinomas (98). NBR1 (Neighbor of Brca1), a cargo receptor responsible for MHC-I degradation through the autophagy-dependent mechanism, was found to be a potential drug target in pancreatic ductal adenocarcinoma (PDAC) (99). An improved analog of indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor, YH29407, has improved T cell infiltration and tumor antigen presentation in murine colorectal carcinoma models (100). Although current studies have demonstrated the therapeutic potential in modulating antigen presentation, more research needs to be done to provide a more robust foundation for treating different tumor types, thereby opening more avenues for personalized medicine.

The association between TCM and immunotherapy (focusing on antigen presentation)

Atractylenolide I (ATT-I) is a sesquiterpene lactone compound found in *Atractylodes macrocephala Koidz*. Emerging evidence suggests that ATT-I exhibits antitumor effects in various cancer types, including colorectal cancer, melanoma, ovarian cancer, and breast cancer (37,101-104). Recent studies from our group have revealed that binding of natural ATT-I compound with proteasome 26S subunit non-ATPase 4 (PSMD4) stabilizes the immunoproteasome in tumor cells. The stabilization resulted in enhanced MHC-I mediated antigen presentation in tumor cells, thus, triggering CTLs cytotoxicity and killing in the colorectal cancer cell model. Our study also demonstrated enhanced efficacy of ICB therapy by combining ATT-I and PD-1 monoclonal antibody (mAb) in the murine colorectal carcinoma model (37). In breast cancer, ATT-I suppressed tumor growth and

metastasis by inhibiting the Toll-like receptor 4 (TLR-4) mediated NF-kB signaling pathway (101). ATT-I has been reported to involve in cell cycle arrest and apoptosis in melanoma and ovarian cancer cells. ATT-I-treated B16 melanoma cells had an increased p21, an indicator for cell cycle arrest, and a decreased CDK2 expression, a key cell cycle progression promoter. Overall, these effects impede cycle cell progression beyond the G1 phase. Furthermore, ATT-I-treated B16 melanoma cells exhibited increased apoptosis activity via increased p53 and decreased ERK/GSK3β signaling (103). In contrast, the effects of ATT-I in A2780 cells, a human ovarian cell line, appeared to be different from that of melanoma cells. ATT-I-treated A2780 cells showed cell cycle arrest in the G2/M phase transition, which was induced by decreased expressions of cyclin B1 and CDK1. In addition, enhanced apoptosis in ATT-I-treated A2780 cells resulted from the altered PI3K/Akt/mTOR pathway (102). An interesting point arose from these studies as the same compound might target multiple cell cycle checkpoints to exert similar inhibitory effects. Thus, more investigations of these pathways and effects on cell cycles by ATT-I should be conducted to delineate whether different mechanisms are involved in distinct types of cancer when treated by ATT-I.

Curcumin is a natural, non-toxic polyphenol substance isolated from the rhizomes of *Curcuma longa*, *Curcuma zedoaria*, and *Acorus calamus L* (105). Supported by extensive studies, curcumin has many pharmacological benefits, such as anti-inflammatory, anti-cancer and immunomodulatory effects (106-111). Many mechanisms of action of curcumin have been proposed and investigated. STAT3 plays a vital role in the receptor tyrosine kinase pathway, which regulates gene transcription. Consecutive activation of STAT3 is observed in many cancer types. Curcumin has been reported to augment *in vivo* enhancement of CTLs through rejuvenating DCs by directly inhibiting STAT3, a key modulator in the tyrosine kinase pathway with known consecutive activation in many cancer types. In addition, combining curcumin with PD-1/PD-L1 checkpoint blockade agents demonstrated synergistic antitumor effects in murine tumor models (112). In another study, low-dose curcumin revealed an enhanced CTL-mediated antitumor immunity targeting 3LL tumor cells, a Lewis lung carcinoma cell line, by increasing IFN-γ secretion and proliferation of CTLs (108). In head and neck squamous cell carcinoma, curcumin was postulated to downregulate the expression of immune checkpoint (IC) ligands such as PD-L1, PD-L2, and Galectin-9, leading to reduced epithelial-to-mesenchymal transition, restored CTLs cytotoxicity, and reduced $CD4^+CD25^+FoxP3^+$ Treg cells within the solid TME (109). Despite these promising therapeutic effects, natural curcumin extract has limited utility due to its poor water solubility and stability. A recent study has focused on designing and examining curcumin analogs. One example was GO-Y030, a curcumin analog that limited the immunosuppressive function of Treg cells by inhibiting their mTOR-S6 axis (107).

Recently, more TCM compounds have been investigated in the cancer immunotherapy field. Artesunate, is derived from a natural compound, artemisinin. Artemisinin is extracted from *Artemisia annua* and is used to treat malaria. Recently, Artesunate has also been identified as a potent anti-cancer candidate. It inhibits TAZ/PD-L1 signaling in non-small cell lung cancer (113). Other small molecule compounds extracted from a TCM called *Huangqin* have been extensively analyzed in Cai *et al.*'s *in silico* study (114). In short, based on their analysis, baicalin, wogonin, and oroxylin A are the bioactive ingredients in *Huangqin*, which claim to promote anti-tumor immunity. However, these studies have only been preliminary, and more research is needed to validate the efficacy and therapeutic utility of those small molecule compounds.

A general concern about using TCM lies in the poor water solubility, purity, and low efficacy when used in smaller quantities. Thus, analogs of TCM should be explored and assessed to improve the solubility and efficacy of these small molecular compounds to enhance their clinical utility.

Conclusions

It is challenging to treat solid tumors with current immunotherapy strategies due to their complex TME and other factors involved in the targeted killing. However, ample evidence has suggested that enhanced antigen presentation by the tumor cells can be a promising way to induce cytotoxicity by the $CD8^+$ effector T cells, thereby leading to tumor shrinkage and clinical remission. The precise antigen processing and presentation mechanism in cancer cells are still unclear. A deeper understanding into such pathways would offer more insight into the heterogeneous nature of the antigenicity and immunogenicity of tumor cells. Furthermore, more research is needed to figure out if there are possible small molecule inhibitors that could potentiate the MHC-I antigen presentation pathway in tumor cells to enhance the

cytotoxicity of CTLs and accelerate tumor apoptosis.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://lcm.amegroups.com/article/view/10.21037/lcm-23-5/coif). XL has a pending international patent application No. PCT/US2021/061295, entitled "Methods to sensitize cancer cells to immune attack using atractylenolide". XL serves as an unpaid editorial board member of *Longhua Chinese Medicine* from September 2022 to August 2024. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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