XBP1 signaling from tumor metabolic stress to myeloid driven immunotherapy resistance (Review)

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Abstract. The tumor microenvironment (TME) is a complex ecosystem with harsh conditions, such as hypoxia, nutrient deprivation, metabolic acidosis and oxidative stress, that promote tumor progression and shape immune responses. In this environment, endoplasmic reticulum stress and the unfolded protein response are activated, with the transcription factor X-box binding protein 1 (XBP1) serving a key role. XBP1 not only maintains cell protein homeostasis, but also modulates the generation, metabolic adaptation and immunosuppressive function of myeloid-derived suppressor cells (MDSCs). The TME and tumor-derived factors, such as exosomes, remotely activate XBP1 in MDSCs, enhancing their survival and immunosuppressive capability by reprogramming lipid and glucose metabolism and upregulating the expression of arginase-1, inducible nitric oxide synthase, reactive oxygen species and immunosuppressive cytokines. The present review aimed to describe the TME stress-XBP1-MDSC-immunosuppression axis, its molecular mechanisms and the role of XBP1 in MDSC heterogeneity and plasticity. Targeting XBP1 may enhance the efficacy of existing therapies, particularly immune checkpoint blockade, by alleviating MDSC-mediated immunosuppression, offering a novel paradigm for understanding and reversing tumor immune escape.

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Contents

1. Introduction

The malignant progression of a tumor involves complex ecological shifts in the tumor microenvironment (TME) (1). The TME is a heterogeneous and dynamically changing pathological environment, characterized by adverse physical and chemical conditions (2). The rapid growth of solid tumors typically exceeds their blood supply capacity, resulting in extensive and persistent hypoxic areas (3,4). To meet the energy and biosynthesis requirements for solid tumor proliferation, tumor cells tend to undergo high-speed glycolysis (Warburg effect) even under aerobic conditions (5,6). However, this reaction depletes key nutrients such as glucose and produces large quantities of lactic acid, causing local acidosis (7,8). In addition, the competitive consumption of amino acids, changes

in osmotic pressure and accumulation of metabolic waste constitute an unfavorable environment for normal cells (9). However, tumor cells and their recruited stromal and immune cells do not perish in this harsh environment, but instead evolve stronger adaptive mechanisms. Endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) are key mechanisms by which cells respond to TME stress (10,11). The ER is a key organelle responsible for secreting proteins, folding membrane proteins, synthesizing lipids and storing calcium ions. Hypoxia, nutritional deficiency (particularly glucose) and acidosis disrupt the homeostasis of the ER, leading to accumulation of unfolded or misfolded proteins in the ER cavity, thereby inducing ER stress (12,13). To restore the homeostasis of the ER, cells initiate the UPR mediated by three primary signaling pathways: Inositol-requiring enzyme (IRE)1α, protein kinase R-like ER kinase and activating transcription factor 6 (14,15). These pathways alleviate the burden on the ER by decreasing overall protein translation, enhancing the expression of ER chaperone proteins and promoting the degradation of misfolded proteins. If ER stress persists or becomes too intense, the UPR shifts from promoting cell adaptation to promoting cell death, or activates transcriptional programs that promote cell survival, inflammation, angiogenesis and metastasis (16,17). Therefore, the UPR has evolved from a protein quality control system to a key signaling platform that integrates multiple environmental pressures and coordinates tumors and their microenvironmental adaptive responses.

In the complex immune cell population of the TME, myeloid-derived suppressor cells (MDSCs), the primary component of the immune suppression network, have attracted great attention (18,19). MDSCs are a group of heterogeneous, immature myeloid cells whose normal terminal differentiation is systematically blocked in pathological states such as tumors, chronic inflammation or infection, leading to their extensive expansion in the bone marrow, spleen and peripheral blood and specific recruitment to the tumor site (20). Based on differences in cell phenotype, morphology and function, MDSCs are primarily divided into two categories: Granulocyte- (with a phenotype close to neutrophils, typically $CD11b^+$ lymphocyte antigen 6 complex, locus G (Ly6G)-positive, Ly6Ch-low and monocyte-like MDSCs (a phenotype close to monocytes, usually $CD11b^+$ $Ly6G^-$ $Ly6Ch^{high}$) (21,22). These types of MDSC play an important role in driving tumor immune evasion and resistance to multiple types of therapy through both overlapping and complementary mechanisms: They express arginase-1 (Arg-1) and inducible nitric oxide synthase (iNOS) at high levels, respectively, consuming the essential amino acid L-arginine for T cell function and producing cytotoxic NO, leading to inhibition and dysfunction of T cell proliferation (23,24). They also generate a large quantity of reactive oxygen species (ROS), disrupt T cell receptor signaling and induce T cell apoptosis (25,26). In addition, MDSCs secrete immunosuppressive cytokines such as IL-10 and transforming growth factor (TGF)-β, which inhibit dendritic cell (DC) function, promote the generation and function of regulatory T cells and directly inhibit T cell activity by upregulating checkpoint molecules such as programmed cell death ligand-1 (PD-L1) (27). The accumulation of MDSCs is associated with poor prognosis, metastasis progression and resistance to chemotherapy and radiotherapy (particularly immune checkpoint blockade therapy) in a variety of solid tumors and hematological malignancies (28-30).

A key question is how the stress state and adaptation mechanism of tumor cells (particularly ER stress/UPR) transcend cellular boundaries, transform into functional regulation of immune cells such as MDSCs in the TME, and actively construct and maintain an immunosuppressive ecosystem conducive to their own survival and development. Accumulating evidence suggests that the connection between tumor cells and MDSCs is not limited to chemokine recruitment, but also involves complex metabolite exchange (13), signaling molecule transmission and epigenetic reprogramming (19). The ER stress/UPR pathway, particularly its most conservative and signal-rich branch [the IRE1α-X-box binding protein 1 (XBP1) signaling axis], is a key messenger and effector of this cross-cellular regulation (31,32). The present review aimed to describe a novel integrated framework: The TME stress XBP1 MDSC immune evasion axis. Previous research has shown that stresses in the TME directly act on MDSCs, activating their intrinsic XBP1 program, and tumor cells also remotely activate and maintain XBP1 activity in MDSCs by releasing soluble factors and extracellular vesicles such as exosomes (33-35). Once activated, XBP1 is a key mediator in regulating the function of MDSCs, shaping the immunosuppressive phenotype of MDSCs through multidimensional mechanisms, including driving metabolic reprogramming, enhancing cell activity and directly regulating the expression of immunosuppressive effector molecules (36,37). (Table I; Fig. 1). Furthermore, the present review aimed to discuss the important therapeutic potential of targeting this axis in reversing immune suppression and overcoming treatment resistance. Through this systematic exposition, the present study aims to provide a novel and unified perspective for understanding the complex interactions of tumor immune metabolism and open up new avenues for developing more effective antitumor immune combination therapy strategies (38-40).

2. XBP1 signaling pathway: From protein homeostasis regulation to immune cell instructions

To understand how XBP1 plays a key regulatory role in MDSCs, it is necessary to explore its molecular regulatory mechanisms and functional network. XBP1 is one of the most extensively studied and functionally diverse transcription factors in the UPR, and its activity is regulated by the upstream sensor IRE1α (41-43).

Molecular switch: IRE1α-mediated unconventional splicing. Under non-stress conditions, XBP1 gene transcription produces unspliced mRNA, which translates into unspliced XBP1 (XBP1u) protein (41,44,45). XBP1u is an unstable protein that contains a rapid degradation signal mediated by a C-terminal domain, resulting in a short half-life. XBP1u has weak transcriptional activity and may serve as a negative regulatory factor for spliced XBP1 (XBP1s) (46-48). When ER stress occurs, activated IRE1α dimerizes and undergoes autophosphorylation, stimulating its site-specific ribonuclease activity (49,50). IRE1α recognizes and cleaves two specific sites on XBP1 mRNA, removing an intron containing 26 nucleotides (41,51).

Table I. Evidence for XBP1-mediated mechanisms in MDSCs and related cell types.

Mechanism/function	Category	Cell type/context	(Refs.)
XBP1 activation drives MDSC immunosuppressive function via upregulation of Arg1, iNOS and ROS production	Direct evidence (experimentally validated in MDSCs)	MDSCs: Directly demonstrated in tumor-infiltrating MDSCs (ovarian cancer models)	(23,117,138,139)
XBP1 regulates lipid accumulation and metabolic adaptation, promoting MDSC survival and suppressive capacity in the TME	Direct evidence (experimentally validated in MDSCs)	MDSCs: Validated in MDSCs; XBP1 deficiency impairs lipid metabolism and survival	(55,80,115)
Tumor-derived factors (exosomes, metabolites) remotely activate XBP1 in MDSCs	Direct evidence (experimentally validated in MDSCs)	MDSCs: TME stress signals are transmitted to MDSCs to trigger XBP1	(103,108,110)
XBP1 deficiency in MDSCs enhances anti-tumor T cell responses and improves immunotherapy efficacy	Direct evidence (experimentally validated in MDSCs)	MDSCs: Validated in conditional knockout mouse models	(13,30,107)
XBP1 regulates inflammatory cytokine production (IL-6, TNF-α) and drives macrophage polarization (M1/M2)	Indirect evidence (extrapolated from macrophages, DCs or tumor cells)	Macrophages: Well-established in macrophages; hypothesized to contribute to M-MDSC suppressive phenotypes	(32,73,77)
XBP1 is key for the development, survival and antigen-presenting function of classical DCs and plasma cells	Indirect evidence (extrapolated from macrophages, DCs or tumor cells)	DCs/B cells: Validated in DCs; hypothesized role in MDSC differentiation block	(13,60,67,68)
XBP1 promotes cell survival, angiogenesis and metastasis under hypoxic and severe ER stress conditions	Indirect evidence (extrapolated from macrophages, DCs or tumor cells)	Tumor cells: Extensively demonstrated in cancer cells; suggests how MDSCs survive harsh TME conditions	(12,85,121)
XBP1 modulates glucose metabolism and high-speed glycolysis to meet bioenergetic demands	Indirect evidence (extrapolated from macrophages, DCs or tumor cells)	Tumor cells/macrophages: Proven in tumor cells and macrophages; indirect evidence for MDSC metabolic reprogramming	(57,89)
Specific crosstalk and compensatory mechanisms between XBP1 and other UPR branches (PERK, ATF6) within MDSC subsets	Hypothetical (requires future validation in MDSCs)	MDSCs: While UPR crosstalk exists in other cells, subset-specific (PMN-MDSC vs. M-MDSC) dynamics remain unproven	(41,42,61)
Direct epigenetic or post-translational regulation of XBP1 target genes controlling MDSC plasticity	Hypothetical (requires future validation in MDSCs)	MDSCs: Extrapolated from general epigenetic studies; lacks direct MDSC-specific validation	(76,131,135)
Role of XBP1 in regulating mitochondrial dynamics (fission/fusion) and fatty acid oxidation pathways in MDSCs	Hypothetical (requires future validation in MDSCs)	MDSCs: Inferred from XBP1 role in mitochondrial function in other cell types	(81,88,116)
Feasibility and safety of pharmacologically targeting XBP1 in MDSCs *in vivo* without causing systemic immunotoxicity	Hypothetical (requires future validation in MDSCs)	Systemic XBP1 inhibition affects multiple cell types; MDSC-specific targeted delivery remains speculative	(39,101,102)

XBP1, X-box binding protein 1; M-MDSC, monocytic myeloid-derived suppressor cell; Arg-1, arginase-1; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; TME, tumor microenvironment; DC, dendritic cell; ER, endoplasmic reticulum; UPR, unfolded protein response; PERK, protein kinase R-like; ATF6, activating transcription factor 6; PMN, polymorphonuclear.

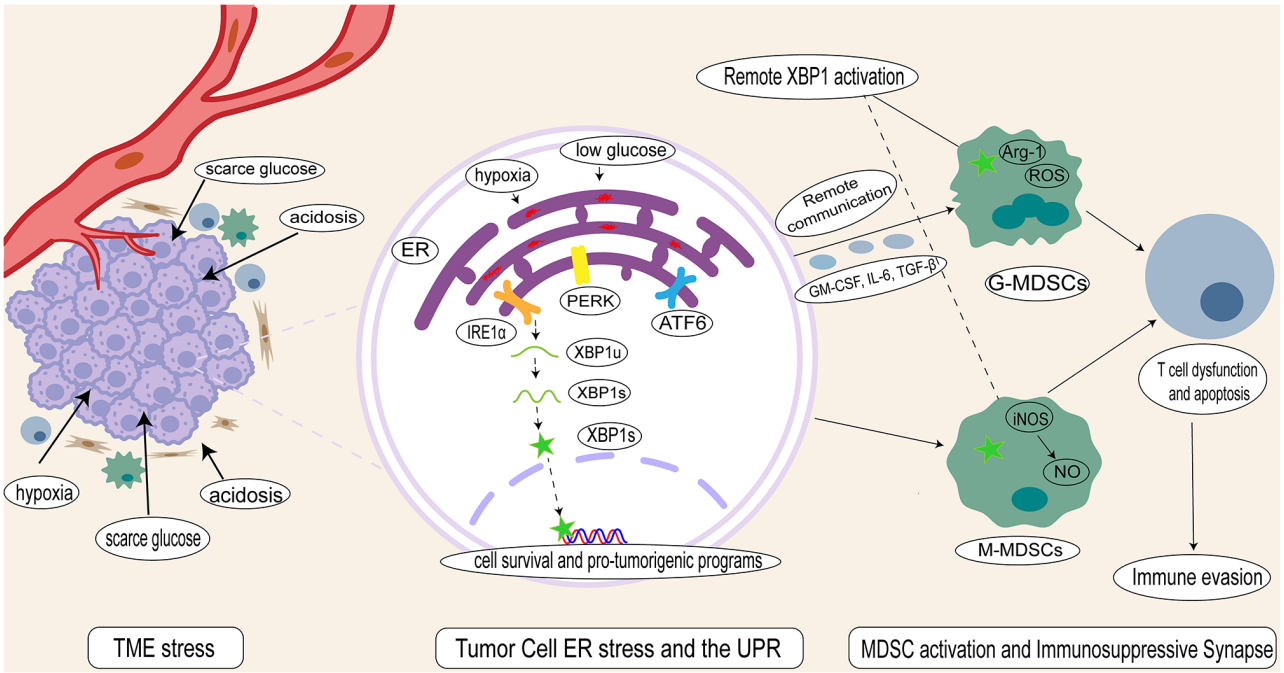

Figure 1. Association between TME and ER stress and MDSC-mediated immunosuppression. Hypoxic, acidic and glucose-deprived conditions in the TME induce ER stress and activate the IRE1α/XBP1 pathway in tumor cells. XBP1s promotes tumor cell survival and remotely activates G- and M-MDSCs via factors such as GM-CSF, IL-6 and TGF-β, leading to the expression of Arg-1, ROS, iNOS and NO, which suppress T cell function and facilitate immune evasion. Solid lines, directly validated in MDSCs; dashed lines, inferred from other cell types (macrophages, tumor and dendritic cells). TME, tumor microenvironment; ER, endoplasmic reticulum; G-MDSC, granulocytic myeloid-derived suppressor cell; IRE, inositol-requiring enzyme 1; XBP1s, spliced X-box binding protein 1; M-, monocytic; GM-CSF, granulocyte-macrophage colony-stimulating factor; Arg-1, arginase-1; ROS, reactive oxygen species; iNOS, inducible nitric oxide synthase; u, unspliced; ATF6, activating transcription factor 6; PERK, protein kinase R-like ER kinase; UPR, unfolded protein response.

This unique and spliceosome-independent unconventional splicing event results in a frameshift in the mRNA reading frame (15,52). The spliced mRNA is ligated and translated to produce a stable protein: XBP1s (53,54). In XBP1s, the C-terminal degradation domain of XBP1u is replaced by a potent transcriptional activation domain, while the N-terminal basic leucine zipper domain is retained, enabling it to exist stably and efficiently bind to DNA (55-57).

Roles of XBP1. As a transcription factor, the classical target gene profile of XBP1 primarily involves maintaining and enhancing ER function and biosynthesis and protein folding capacity expansion. XBP1s directly upregulates a number of genes encoding ER resident chaperones (such as Glucose-Regulated Protein 78/Immunoglobulin Heavy-Chain Binding Protein, GRP94, calnexin and calreticulin) and folding enzymes (such as members of the protein disulfide isomerase family), thereby enhancing the ability of the ER to process unfolded protein loads (58,59).

XBP1s is a key transcriptional regulator that modulates the lipid synthesis pathway. It not only directly regulates the expression of enzymes such as fatty acid synthase and acetyl coenzyme A (CoA) carboxylase, but also promotes lipid biosynthesis and ER membrane expansion by regulating genes associated with phospholipid synthesis and sterol regulatory element-binding protein processing and activation, providing key membrane structural components for cell proliferation and secretion (60,61).

XBP1s upregulates genes encoding ER Golgi apparatus intermediate compartment components, vesicle transport-associated proteins and various enzymes and transporters in the protein secretion pathway, thereby enhancing the overall protein secretion ability of cells. Notably, XBP1s also upregulates its own pathway components, such as IRE1α, in a positive feedback manner, forming a self-adaptive loop (62,63). These functions establish XBP1 as a crucial mediator of cellular metabolism and secretion pathways. The regulatory network of XBP1 extends beyond ER-associated genes to interact with multiple key signaling pathways and transcription factors, thereby participating in a wide range of biological processes. For example, XBP1s can interact with the NF-κB pathway to regulate the expression of inflammatory factors (64), collaborate with hypoxia-inducible factor (HIF)-1α to regulate hypoxia adaptation genes and participate in regulating the expression of autophagy- and apoptosis-associated genes (65,66). In immune cells, XBP1 serves a key role in B cell differentiation, plasma cell antibody secretion, DC antigen presentation and the macrophage inflammatory response (67-69).

From steady state maintainer to core regulator: Foundation of immune regulation potential. XBP1 serves as a key regulatory factor in the tumor immune ME due to its strong transcriptional regulation ability. The regulation of XBP1 is aimed at reshaping the overall metabolic pattern of cells by regulating key nodes of glucose, lipid and amino acid metabolism, changing the energy acquisition mode and biosynthetic flow of immune cells and providing necessary material support for cell functional transformation (36,70). XBP1 drives metabolic reprogramming of MDSCs in mouse lung cancer models by

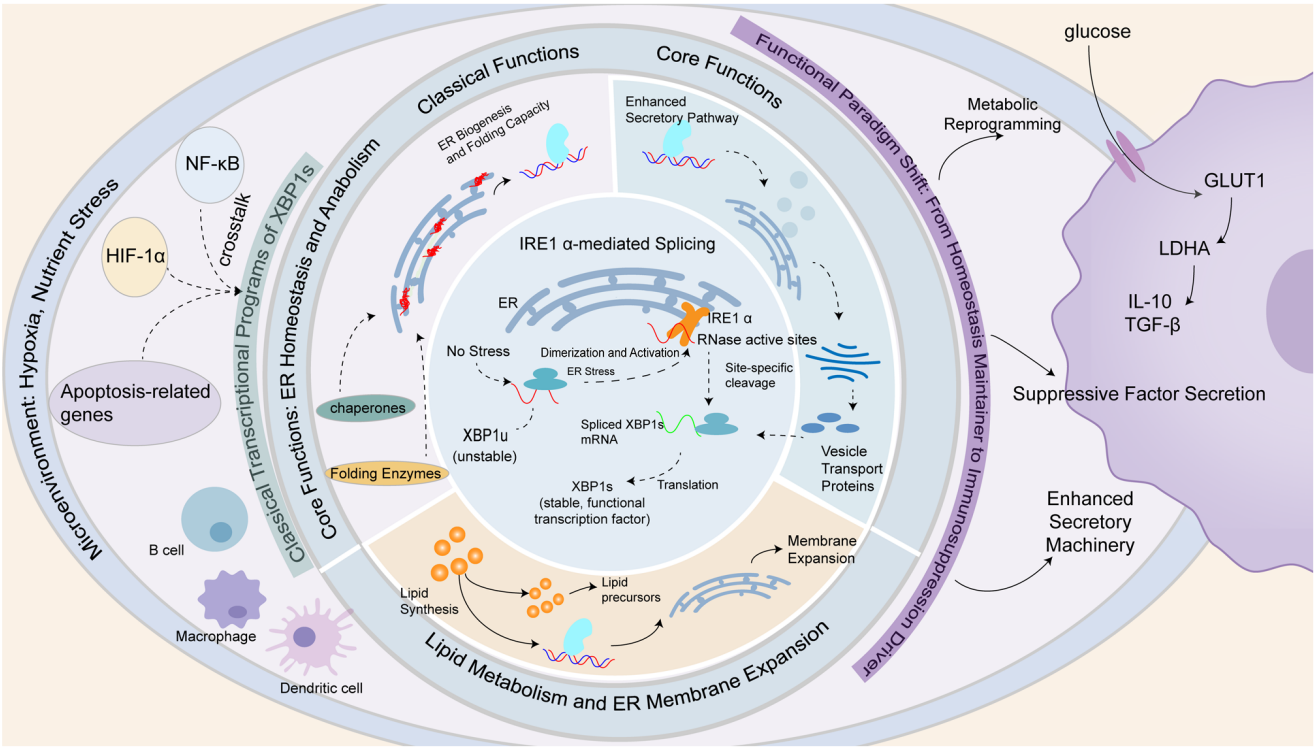

Figure 2. Activation and functional network of the XBP1 signaling pathway. XBP1s serves as a central transcription factor that orchestrates cellular adaptation to ER stress. It upregulates chaperones, lipid synthesis enzymes and secretory pathway components, while also interacting with HIF-1α, NF-κB and apoptosis-related genes to regulate metabolism, survival and immune responses. XBP1 serves a dual role in maintaining ER homeostasis and driving pro-tumorigenic programs. Solid lines, directly validated in MDSCs; dashed lines, inferred from other cell types (macrophages, tumor cells, DCs). XBP1s, spliced X-box binding protein 1; ER, endoplasmic reticulum; HIF, hypoxia-inducible factor; MDSC, monocytic myeloid-derived suppressor cell; IRE, inositol-requiring enzyme 1; GLUT, glucose transporter; LDHA, lactate dehydrogenase A.

upregulating the expression of key glycolytic enzymes, glucose transporter 1 (GLUT1) and lactate dehydrogenase A (71,72). It also regulates the expression of key immune-associated genes, which directly or indirectly affects the transcription levels of effector molecules such as cytokines, chemokines, iNOS and immune checkpoint molecules (73,74). Furthermore, it strengthens the secretion function of cells by enhancing the transport efficiency of secretion pathways, ensuring the effective output of these immune regulatory proteins and thereby amplifying the paracrine regulatory effect of cells (60).

Under the stress background of the TME, the XBP1 signaling program within MDSCs is continuously activated by abnormal stress signals from tumor cells and the ME (13). This abnormal activation directly leads to the physiological function of XBP1 being redirected and the original survival promoting function is instead used to support the abnormal accumulation of MDSCs in harsh conditions, such as hypoxia and nutrient deficiency (75). The metabolic reprogramming ability is adapted to the high energy consumption requirements of MDSCs to exert immunosuppressive functions, while the enhanced secretion function is used to synthesize and release a large quantity of immunosuppressive factors such as IL-10 and TGF-β (76). This indicates that XBP1 undergoes a functional paradigm shift in MDSCs, from an internal environment homeostasis regulatory molecule to a functional regulatory factor that drives immune suppression and mediates tumor progression (77). This functional transformation establishes the regulatory axis of tumor stress-XBP1 MDSCs. Preclinical studies have shown that blocking XBP1 signaling can weaken the immunosuppressive activity of MDSCs and enhance the efficacy of tumor immunotherapy (36,78) (Fig. 2).

3. Stress signals in the TME: Activation of the XBP1 program in MDSCs

The immunosuppressive ability of MDSCs is not innate, but dependent on the action of the TME. The key step in this process is the activation of the XBP1 program within these cells (79). The initiation signals derive from a range of sources, including direct effects from the physical and chemical conditions of the TME, as well as molecular signals actively issued by tumor cells (80).

Extracellular stressors: Direct impact of the TME. Hypoxia is one of the primary characteristics of the TME. Oxygen is involved in the formation of disulfide bonds in proteins; under hypoxic conditions, the folding function of oxidized proteins is directly impaired. At the same time, there is a change in cell energy supply, namely ATP production, which triggers ER stress. The key transcription factor HIF-1α, regulated by hypoxia, exhibits cross-regulation with the UPR pathway (81). Hypoxia directly activates the IRE1α-XBP1 axis, while XBP1s can exhibits co-regulation with HIF-1α through protein level interactions or co-binding target gene promoter regions (82). The activity of the IRE1α-XBP1 axis in myeloid cells is key for HIF-1α-dependent hypoxia responses and regulates the

production of cytokines such as IL-1β and IL-6 to adapt to hypoxic environments (83). Typically, both XBP1s and HIF-1α upregulate the expression of multiple key genes in the glycolysis pathway, which markedly enhances the metabolic adaptability of MDSCs to hypoxic environments. At the same time, it may promote the transcriptional activation of immune suppressive phenotype-associated genes. HIF-1α deficiency significantly decreases the expression of Arg-1 and iNOS in MDSCs, weakening their immune suppressive function (84-86). In addition to XBP1, other metabolic key regulators such as pyruvate kinase isozyme type M2 are also activated in TME hypoxia and glucose deficiency, and promote the recruitment and function of MDSCs by driving glycolysis and cytokine secretion (87).

Glucose competition is intense in the TME and MDSCs are often in a glucose starvation state. Glucose deprivation causes a dual stress attack on cells, leading to insufficient ATP synthesis and an energy crisis, as well as affecting the protein N-linked glycosylation process, causing misfolded proteins to accumulate in the ER and a folding crisis. These drive the activation of the IRE1α/XBP1 pathway, and sustained IRE1α activation induces XBP1 mRNA splicing to form functional transcription factors, which enhance ER chaperone protein gene transcription to cope with stress (41,88). To maintain survival and function, MDSCs activate alternative energy harvesting mechanisms. The XBP1-mediated lipid synthesis pathway serves a key role in this process, as the synthesized lipids provide structural materials for cell membrane proliferation and products such as fatty acids can be oxidized to produce ATP through mitochondrial β-oxidation or stored in lipid droplets as energy reserves (89). MDSCs require a large quantity of glucose and fatty acids as energy sources, and the reshaping of their metabolic patterns is directly associated with their immunosuppressive function (36). Therefore, XBP1 is a key regulatory node for MDSCs to achieve metabolic conversion in glucose-deficient environments.

Marked accumulation of lactate in the TME is not only due to the accumulation of metabolic byproducts, but also serves as an active signaling molecule, metabolic substrate and epigenetic regulator-involved in the remodeling of the intra- and extracellular environment. Traditionally, lactate has been considered as the end-product of glycolysis, but previous research has revealed its active regulatory role in immune regulation and stress signal transduction (90). Tumor cells continuously produce lactate through aerobic glycolysis, which lowers the extracellular pH to <6.5. This acidic environment not only inhibits T cell infiltration and function, but also directly interferes with the ion balance of neighboring cells. The abnormal proton gradient on both sides of the cell membrane leads to sustained activation of Na^+/H^+ exchangers, which causes disruption of intracellular calcium homeostasis. As the primary calcium storage site of cells, the ER abnormally opens the Ryanodine receptor and Inositol 1,4,5-Trisphosphate Receptor (IP3R) channels under acidosis, leading to the non-physiological release of Ca^{2+}. This has been verified by the fluorescent probe Fura-2 in the breast cancer MCF-7 cell model (91). When intracellular calcium fluctuations exceed the cell buffering capacity, the resulting stress drives the sustained activation of the IRE1α/XBP1 branch of the UPR (92). In addition, a low-pH environment directly affects the three-dimensional conformational stability of proteins, with a key impact on secreted proteins rich in disulfide bonds. The shift of redox potential within the ER leads to restricted function of Protein Disulfide Isomerase (PDI) family molecular chaperones and the accumulation of misfolded proteins increases the burden on the ER. Under these conditions, MDSCs exhibit upregulation of Arg-1 and iNOS expression and their enhanced immunosuppressive activity is not solely dependent on lactate receptor GPR81 signaling, suggesting the existence of other acidic environment sensing mechanisms (93). To the best of our knowledge, there is no direct evidence to suggest that XBP1 cleavage activation is the result of proton concentration changes transmitted through specific receptors. However, chromatin immunoprecipitation-sequencing (seq) data show that acid exposure can increase the binding frequency of XBP1 to target gene promoter regions, involving classical ER stress markers such as endoplasmic reticulum oxidoreductin (ERO1α) and Binding Immunoglobulin Protein (47,94). Treating acidosis as an independent stressor rather than a metabolic outcome provides a new approach for the study of targeted tumor immune escape mechanisms (95,96).

Tumor-derived signals: Active programming of tumor cells. The interaction of cytokine networks is a key link in the construction of an immunosuppressive ME in tumors. The cytokines secreted by tumor cells serve a key regulatory role, among which granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, IL-1β and vascular endothelial growth factor directly drive the expansion, recruitment and survival of MDSCs, as well as downstream activated signaling pathways such as Janus kinase/STAT3 and NF-κB, which have been shown to form multi-level cross regulatory interactions with the UPR pathway (97-100). The sustained activation of STAT3 is a key regulatory event for MDSCs to acquire expansion ability and immune suppression function. ER stress induces STAT3 activation (101,102). Certain cytokine signaling also reciprocally enhances the activity of the IRE1α/XBP1 pathway. This bidirectional positive feedback regulation mode provides a foundation for the sustained activation and functional enhancement of the XBP1 program in MDSCs (103,104).

The remote delivery of stress signals mediated by tumor extracellular vesicles and soluble factors is a key mechanism for tumor manipulation of distant cells. Tumor cells package their activated stress signals into exosomes, achieving precise regulation of target cells (105-107). For example, exosomes carrying catalytically active IRE1α protein directly initiate XBP1 mRNA cleavage in recipient MDSCs without primary ER stress (108,109). Similarly, exosome-enriched microRNAs (miRs) such as miR-30a maintain XBP1 signaling by targeting its negative regulators (110,111). Furthermore, exosomes can directly transfer the active XBP1s mRNA to propagate the UPR in myeloid cells (112).

Beyond exosomal nucleic acids and proteins, lipids represent another critical class of tumor-derived factors. Cancer cell-intrinsic XBP1 drives the release of cholesterol into the TME, which induces lipid accumulation and immunosuppressive reprogramming in recipient MDSCs (36). This remote activation exhibits cancer-type specificity. While tumor-derived

Table II. Tumor-derived factors and exosomal cargo triggering XBP1 activation and immunosuppressive reprogramming in MDSCs/myeloid cells.

Tumor-derived factor/exosomal cargo	Cargo category	Target cell	Origin	Mechanism of XBP1 activation and immunosuppressive consequence	(Refs.)
Tumor-derived cholesterol/lipids (driven by cancer-intrinsic XBP1)	Lipids	Intratumoral myeloid cells/ MDSCs	Solid tumors (liver, lung, melanoma)	Cancer cell-intrinsic XBP1 promotes cholesterol production, which is transferred to myeloid cells, driving lipid accumulation, metabolic reprogramming and T cell suppression	(36)
TME hypoxia and lactic acid	Microenvironmental metabolites	MDSCs/DCs	Ovarian cancer/TNBC	Hypoxia and metabolic byproducts coordinate with HIF-1α to sustain IRE1α-XBP1 activation, disrupting immune cell homeostasis and enhancing immune evasion	(13,88)
Tumor-derived IL-6, GM-CSF	Soluble cytokines	PMN- and M-MDSCs	Melanoma	Activates JAK/STAT3 and NF-κB signaling, which cross-talks with the UPR to sustain XBP1 transcriptional activity, driving MDSC expansion and Arg-1 expression	(97-100)
Exosomal IRE1α protein (catalytically active)	Protein	MDSCs	Breast	Exogenous active IRE1α directly initiates XBP1 mRNA cleavage in recipient MDSCs, generating active XBP1s without primary ER stress	(108,109)
Exosomal miR-30a	miR	Macrophages/ MDSCs	Macrophage/ myeloid	Exosomal miRs target negative regulators of UPR or directly modulate XBP1 expression, sustaining XBP1 signaling and altering immunosuppressive cytokine profiles	(110,111)
Exosomal XBP1s mRNA	mRNA	Myeloid cells	ER stress	ER stress induces the packaging of active XBP1s mRNA into exosomes. Upon uptake, it directly propagates the active XBP1 transcriptional program in recipient cells	(112)

XBP1s, spliced X-box binding protein 1; M-MDSC, monocytic myeloid-derived suppressor cell; TME, tumor microenvironment; DC, dendritic cell; TNBC, triple-negative breast cancer; HIF, hypoxia-inducible factor; IRE, inositol-requiring enzyme 1; GM-CSF, granulocyte-macrophage colony-stimulating factor; PMN, polymorphonuclear; UPR, unfolded protein response; Arg-1, arginase-1; miR, microRNA.

cytokines (such as IL-6 and GM-CSF) predominantly drive the STAT3/XBP1 crosstalk to expand MDSCs (97-100), TME hypoxia and lactate coordinate with HIF-1α to hyperactivate the IRE1α-XBP1 axis in ovarian cancer, disrupting DC and MDSC homeostasis (13,88) (Table II).

In summary, the activation and maintenance of high-level activity homeostasis of the XBP1 program in myeloid-derived cells depend on complementary signal inputs in the TME, including stress signals induced by overall ME pressure and molecular regulatory signals actively secreted by tumor cells. The integration of these signals marks the phenotypic remodeling of MDSCs from relatively quiescent immature myeloid precursor to key effector cells adapted to the harsh physicochemical conditions of the TME and possessing immunosuppressive functions (Fig. 3; Table III).

4. XBP1 as a key regulatory mediator of MDSC function: Multidimensional mechanism analysis

Once XBP1 is activated in MDSCs, it coordinates and enhances the immunosuppressive function of MDSCs on multiple interrelated levels.

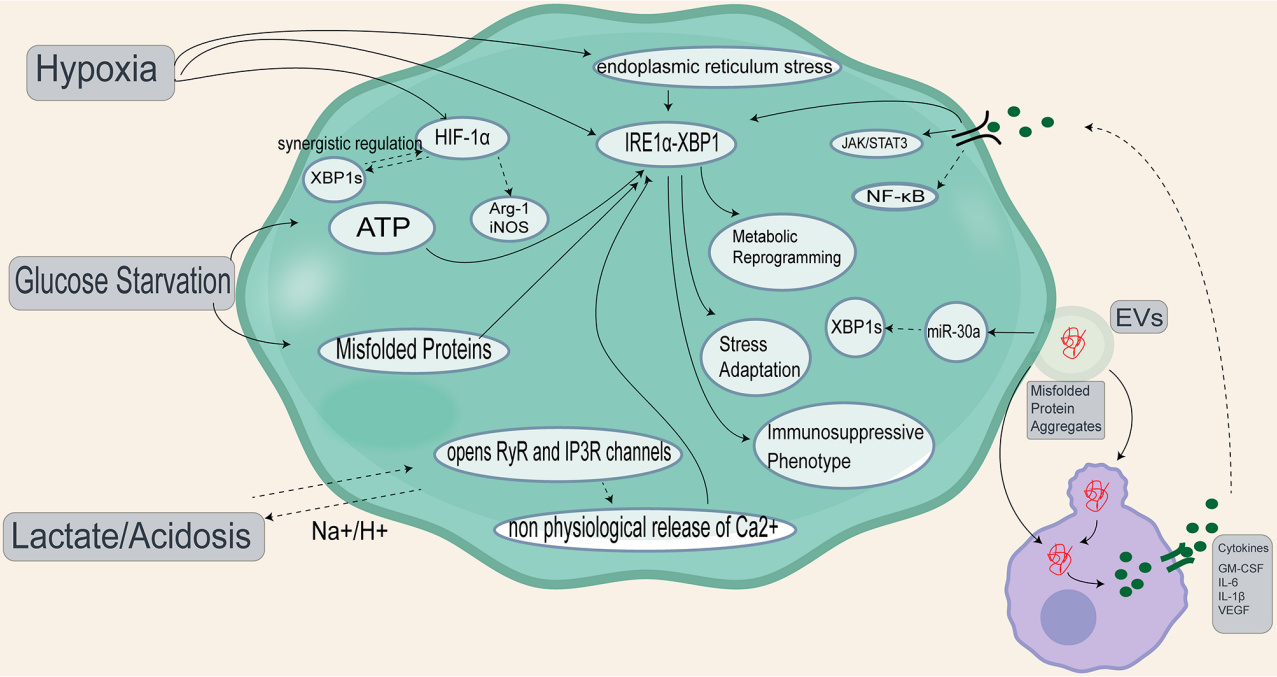

Figure 3. Mechanisms by which TME stress signals activate XBP1 in MDSCs. Hypoxia, glucose starvation and acidosis in the TME induce endoplasmic reticulum stress in MDSCs, leading to IRE1α activation and XBP1 splicing. XBP1s collaborates with HIF-1α, STAT3 and NF-κB to drive metabolic reprogramming, cytokine secretion (GM-CSF, IL-6) and immunosuppressive phenotype acquisition. Tumor-derived EVs and miRs enhance XBP1 activation in MDSCs. Solid lines, directly validated in MDSCs; dashed lines, inferred from other cell types (macrophages, tumor and dendritic cells). TME, tumor microenvironment; XBP1s, spliced X-box binding protein 1; MDSC, monocytic myeloid-derived suppressor cell; IRE, inositol-requiring enzyme; HIF, hypoxia-inducible factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; EV, extracellular vesicle; miR, microRNA; Arg-1, arginase-1; iNOS, inducible nitric oxide synthase; RyR, Ryanodine Receptor; IP3R, Inositol 1,4,5-trisphosphate Receptor.

Promoting the survival, expansion and accumulation of MDSCs. The sustained existence and amplification of MDSCs in the TME are prerequisites for their functional performance (113). Although TME stress induces cell apoptosis, the activation of XBP1 provides a key pro-survival pathway. XBP1s drives the transcription and upregulation of anti-apoptotic proteins, such as Bcl-2 family members (Bcl-2, Bcl-xL and Mcl-1), which inhibit cell apoptosis through the mitochondrial pathway. XBP1 may alleviate the apoptotic tendency that ER stress induces by regulating ER-related apoptotic pathways such CHOP expression (114,115). This anti-apoptotic effect enables MDSCs to survive in TMEs where other immune cells struggle to survive, continuously accumulating and forming physical and functional immunosuppressive barriers. In addition, XBP1 may promote the proliferation of MDSCs by coordinating with other pathways such as STAT3 (116).

Metabolic reprogramming driving MDSCs: Providing energy substrates and biosynthetic precursors for functional execution. Metabolic reprogramming is a key process in which MDSCs acquire immunosuppressive function; the transcription factor XBP1 serves a pivotal regulatory role in this process by directly binding to the promoters of key metabolic genes (13).

XBP1s directly binds to the UPR or ER stress response element in the promoters of genes involved in lipid biosynthesis, such as stearoyl-CoA desaturase 1, diacylglycerol O-acyltransferase 2 and acetyl-CoA carboxylase (117). This direct transcriptional upregulation drives the intracellular lipid accumulation and ER membrane expansion characteristic of MDSCs (118,120). Under hypoxic conditions, XBP1s directly interacts with and stabilizes HIF-1α, co-occupying HIF-1α target promoters to drive aerobic glycolysis (121,122).

Metabolic byproducts serve as the mechanistic link that couples XBP1s-driven metabolic reprogramming with the production of immunosuppressive effectors. Rather than acting as concurrent phenomena, XBP1s-driven metabolic reprogramming promotes the generation of immunosuppressive effectors (Arg-1, iNOS and ROS) through specific metabolic intermediates. XBP1s-driven accumulation of polyunsaturated fatty acids renders MDSCs susceptible to lipid peroxidation, serving as the primary physical source of elevated ROS (118,123,124). Lipid-derived ROS activate the p38 mitogen-activated protein kinase and STAT3 signaling pathways. Activated STAT3 serves as the direct transcriptional activator of the Arg-1 promoter, establishing a causal association between XBP1s-mediated lipid synthesis and Arg-1 upregulation (116,120).

XBP1s-enhanced glycolysis results in high lactate production in the TME (125). Lactate accumulation inhibits prolyl hydroxylases, stabilizing HIF-1α even under normoxic conditions. HIF-1α directly binds the hypoxia-response elements in the promoters of both iNOS and Arg-1, driving their transcription (122,126). XBP1s directly binds the promoter of IL-6, and the subsequent autocrine IL-6 signaling phosphorylates STAT3, which amplifies Arg-1 transcription (116). For iNOS, prolonged IRE1α/XBP1s signaling upregulates CHOP, which heterodimerizes with C/EBPβ to bind the iNOS promoter. Thus, XBP1s orchestrates immunosuppression by using metabolic products (lipid peroxides and lactate) and direct cytokine

Table III. Stress signals in the tumor microenvironment and their potential activation mechanisms on XBP1 in MDSCs.

A, Extracellular stressors

Examples	Potential activation mechanism of XBP1 in MDSC	(Refs.)
Hypoxia	Cross-regulates with the unfolded protein response pathway via HIF-1α to activate the IRE1α-XBP1 axis; XBP1s cooperates with HIF-1α to bind target gene promoters, co-regulating glycolysis pathway genes and immunosuppressive phenotype-associated genes (Arg-1, iNOS)	(81-86)
Glucose deprivation	Triggers an energy (insufficient ATP synthesis) and protein folding crisis (impaired N-glycosylation, accumulation of misfolded proteins), activating the IRE1α-XBP1 pathway; XBP1 mediates the lipid synthesis pathway to provide alternative energy (membrane structural materials/β-oxidation for ATP production) for MDSCs	(36,41,88,89)
Lactate/acidosis	Low pH disrupts cell ion/calcium homeostasis (activation of Na^+/H^+ exchangers, abnormal opening of ER calcium channels), interferes with protein 3D conformation and ER redox potential, driving sustained IRE1α-XBP1 activation; acid exposure enhances XBP1 binding to promoters of target genes such as ERO1α and BiP	(90-96)

B, Tumor-derived signals

Examples	Potential activation mechanism of XBP1 in MDSC	(Refs.)
Cytokines (GM-CSF, IL-6)	Bind receptors on MDSCs to activate pathways such as JAK/STAT3 and NF-κB, which form bidirectional positive feedback regulation with the UPR, maintaining sustained activation of the XBP1 program	(97-100)
Tumor exosomes	Carry active IRE1α protein (directly initiating XBP1 mRNA splicing), miR-30a family (targeting negative regulators of XBP1) or misfolded proteins (inducing ER stress), activating the XBP1 program in MDSCs through multiple pathways	(110)

XBP1s, spliced X-box binding protein 1; MDSC, myeloid-derived suppressor cell; HIF, hypoxia-inducible factor; IRE, inositol-requiring enzyme 1; Arg-1, arginase-1; iNOS, inducible nitric oxide synthase; ER, endoplasmic reticulum; ERO1, endoplasmic reticulum oxidoreductase 1; BiP, heavy-chain binding protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; UPR, unfolded protein response; miR, microRNA.

transcription as mechanistic bridges to activate terminal effectors.

Directly enhancing the expression of immunosuppressive effector molecules: Constructing a key effector molecule system. Building upon the aforementioned metabolic and transcriptional bridges, XBP1s regulates levels of key effector molecules in MDSCs through direct and indirect transcriptional regulation mechanisms (120,127).

While XBP1s directly targets metabolic and cytokine (IL-6) promoters, its regulation of Arg-1 and iNOS is primarily mediated through intermediate transcription factors (STAT3, HIF-1α and CHOP/C/EBPβ). Arg-1 is a key immunosuppressive molecule in MDSCs, the core function of which is to deplete L-arginine in the TME, thereby mediating T cell dysfunction. The XBP1s-lipid peroxidation-ROS-STAT3 and XBP1s-IL-6-STAT3 axes provides the direct transcriptional machinery for Arg-1 upregulation in MDSCs, bypassing the need for XBP1s to bind the Arg-1 promoter directly (116,120,124).

NO produced by iNOS and the ROS produced by NADPH oxidase complexes form a toxic immunosuppressive network. The XBP1s-driven glycolytic flux and lactate production stabilize HIF-1α, which directly drives iNOS transcription via hypoxia-response elements (122,126). In addition to transcriptional regulation, the XBP1s-mediated lipid synthesis provides the necessary membrane lipid ME for the correct assembly and activation of NADPH oxidase complexes, physically enabling ROS generation at the post-translational level (124). XBP1s may also reshape cell redox balance by regulating antioxidant response element-associated genes, such as members of the nuclear factor erythroid 2-related factor 2 pathway, making cells more inclined to promote ROS production rather than clearance (128). Through this multi-tiered regulatory network, XBP1s ensures the sustained output of immunosuppressive effectors.

Regulating the secretion mechanism of immunosuppressive cytokines: Enhancing paracrine effects. MDSCs primarily release immunosuppressive cytokines such as IL-10 and TGF-β through paracrine pathways, which widely inhibit the biological functions of other immune cells in the TME (19,129). The UPR pathway, including its key transcription factor XBP1, is associated with regulating protein secretion processes

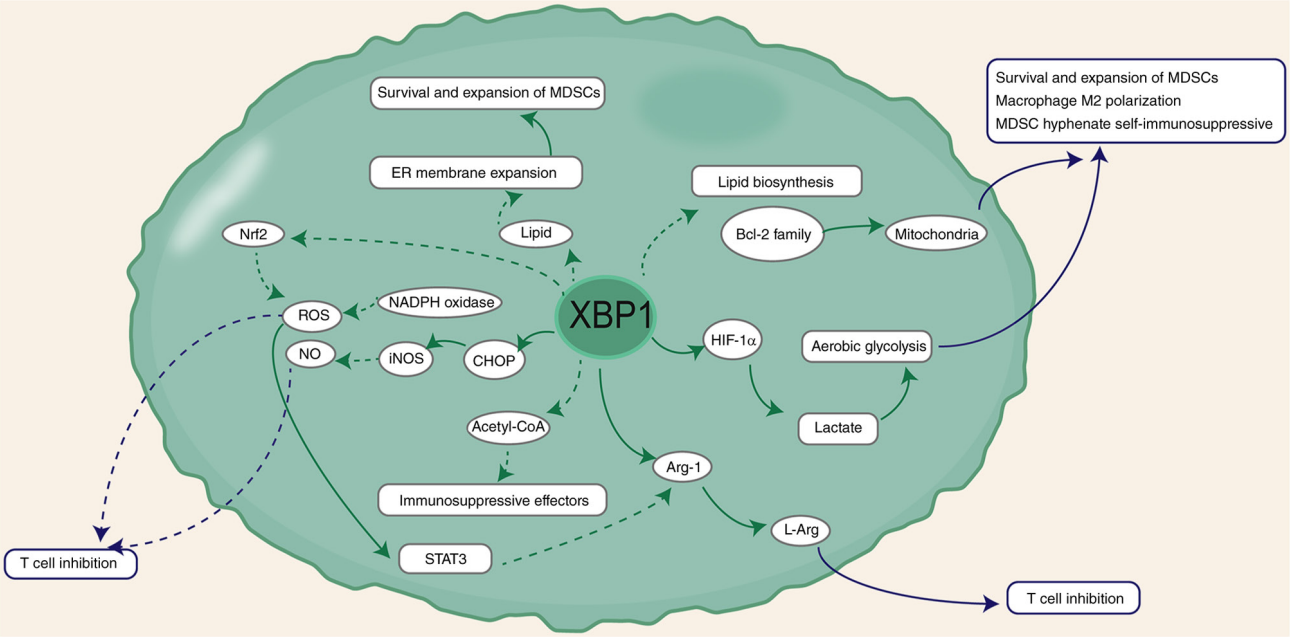

Figure 4. Multidimensional mechanisms of XBP1 in regulating MDSC function. XBP1 promotes MDSC survival and expansion via anti-apoptotic genes (Bcl-2, Mcl-1), drives metabolic reprogramming through lipid synthesis and glycolysis, upregulates immunosuppressive molecules (Arg-1, iNOS, ROS) and enhances cytokine secretion. These integrated mechanisms enable MDSCs to inhibit T cell activation and sustain an immunosuppressive TME. Solid lines, directly validated in MDSCs; dashed lines, inferred from other cell types (macrophages, tumor and dendritic cells). XBP1, X-box binding protein 1; MDSC, myeloid-derived suppressor cell; Mcl-1, myeloid cell leukemia 1; Arg-1, arginase-1; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; TME, tumor microenvironment.

in myeloid cells (15,45). In numerous secretory cell types, activation of XBP1 enhances the ability of the ER to fold and process proteins, as well as Golgi-mediated modification and sorting (45,117). Although direct evidence for MDSCs is limited, previous studies of relevant myeloid populations suggest that UPR activation may enhance the efficiency of immunosuppressive protein secretion, regardless of transcriptional changes (130,131). To the best of our knowledge, whether XBP1 activation increases the secretion of IL-10 or TGF-β by MDSCs without altering their mRNA levels remains to be determined.

Potential mechanisms: Association between MDSC differentiation and polarization. XBP1 may contribute to the functional regulation of MDSCs (120) and previous research highlights the role of long non-coding RNAs in regulating MDSC plasticity in lung cancer (132). The UPR, including its IRE1α/XBP1 branch, is observed in tumor-infiltrating MDSCs (36). In macrophage models (133), XBP1 activation has been shown to promote polarization toward the M2 phenotype (77). Although MDSCs and tumor-associated macrophages (TAMs) exhibit certain immunosuppressive features, to the best of our knowledge, there is currently a lack of direct evidence linking XBP1 to MDSC terminal differentiation or phenotype transformation into TAMs (19,129).

The IRE1α/XBP1 pathway is known to regulate various cell processes, including protein folding, metabolic adaptation and stress responses in various cell types (15,117). Although the role of XBP1 as a key node for coordinating these processes has been established in other secretory cells, its specific contribution to the integrated regulatory network in MDSCs requires direct experimental verification (13) (Fig. 4). Current evidence suggests that the activation of ER stress/UPR is associated with the enhancement of immune suppressive function in MDSCs (127), but whether XBP1 serves as a key node for the specific regulation of this function remains to be determined (Table IV).

5. Heterogeneity and plasticity of XBP1 and MDSCs: Differential impacts on polymorphonuclear (PMN)- and monocytic-MDSCs (M-MDSCs)

MDSCs comprise two notable subsets, PMN-MDSCs and M-MDSCs, which employ distinct immunosuppressive mechanisms (134). A key question is whether XBP1 activation differentially impacts the expansion, survival or trans-differentiation of these specific subsets within the TME. XBP1 does not uniformly affect these populations; rather, it differentially dictates their fate by skewing the expansion of PMN-MDSCs while driving the trans-differentiation of M-MDSCs (36).

Regarding skewing the expansion and survival of PMN-MDSCs, PMN-MDSCs are typically short-lived and rely on lipid metabolism (fatty acid oxidation and lipid droplet accumulation) and Arg-1/ROS for their immunosuppressive function (118,134). XBP1, a master regulator of lipid biosynthesis and ER homeostasis, directly fuels this lipid-dependent metabolic reprogramming (36). By upregulating anti-apoptotic pathways and mitigating ER stress-induced cell death, XBP1 prolongs the lifespan of PMN-MDSCs. Therefore, in the PMN-MDSC compartment, XBP1 activation primarily skews their expansion and accumulation by overcoming their short-lived nature. It maintains their suppressive functionality and delays their clearance,

Table IV. Targets and mechanisms of XBP1 regulating MDSC function.

MDSC functional dimension	Potential key targets/ molecules regulated by XBP1	Functional consequences	(Refs.)
Survival and expansion	Bcl-2 family members (Bcl-2, Bcl-xL, Mcl-1), CHOP, STAT3	Inhibits mitochondrial and ER-associated apoptosis pathways; coordinates with STAT3 to promote MDSC proliferation; enables MDSCs to survive and accumulate in TME, forming immunosuppressive barriers	(113-116)
Metabolic reprogramming	Lipid synthesis- and glycolysis-associated molecules, amino acid transporters/metabolic enzymes (Arg-1), metabolic intermediates (acetyl-CoA)	Enhances lipid synthesis (provides membrane components and energy reserves via β-oxidation); promotes aerobic glycolysis (supplies ATP and biosynthetic precursors); regulates amino acid metabolism (associated with immunosuppressive molecules); mediates epigenetic regulation (reshapes chromatin landscape and stabilizes immunosuppressive phenotype)	(117-126)
Immunosuppressive effector molecules	Arg-1, inducible NO synthase, NADPH oxidase complexes, Nrf2 pathway members	Depletes L-arginine (impairs T cell function); increases NO production (coordinates with ROS to form immunosuppressive networks); facilitates ROS generation (provides membrane lipid ME for NADPH oxidase assembly and regulates redox balance)	(116,120,122,124,126-128)
Immunosuppressive cytokine secretion	IL-10, TGF-β, ER chaperones, Golgi apparatus-associated proteins	Enhances ER folding/processing capacity and Golgi-mediated modification/sorting; improves secretion efficiency of immunosuppressive cytokines; exerts widespread paracrine inhibitory effects on other immune cells in TME	(15,19,45,117,129-131)
Differentiation and polarization	IRE1/XBP1 pathway components	May promote M2-like polarization (based on macrophages); potential role in MDSC terminal differentiation or phenotypic transformation into TAMs (direct evidence pending)	(13,15,19,36,77,117,120,127,129,132)

XBP1, X-box binding protein 1; MDSC, myeloid-derived suppressor cell; ER, endoplasmic reticulum; Mcl-1, myeloid cell Leukemia 1; TME, tumor microenvironment; Arg, arginase; ROS, reactive oxygen species; IRE, inositol-requiring enzyme 1; TAM, tumor-associated macrophages.

rather than inducing trans-differentiation, as PMN-MDSCs are considered terminally differentiated.

Conversely, M-MDSCs possess high developmental plasticity and differentiate into TAMs or DCs (134). In

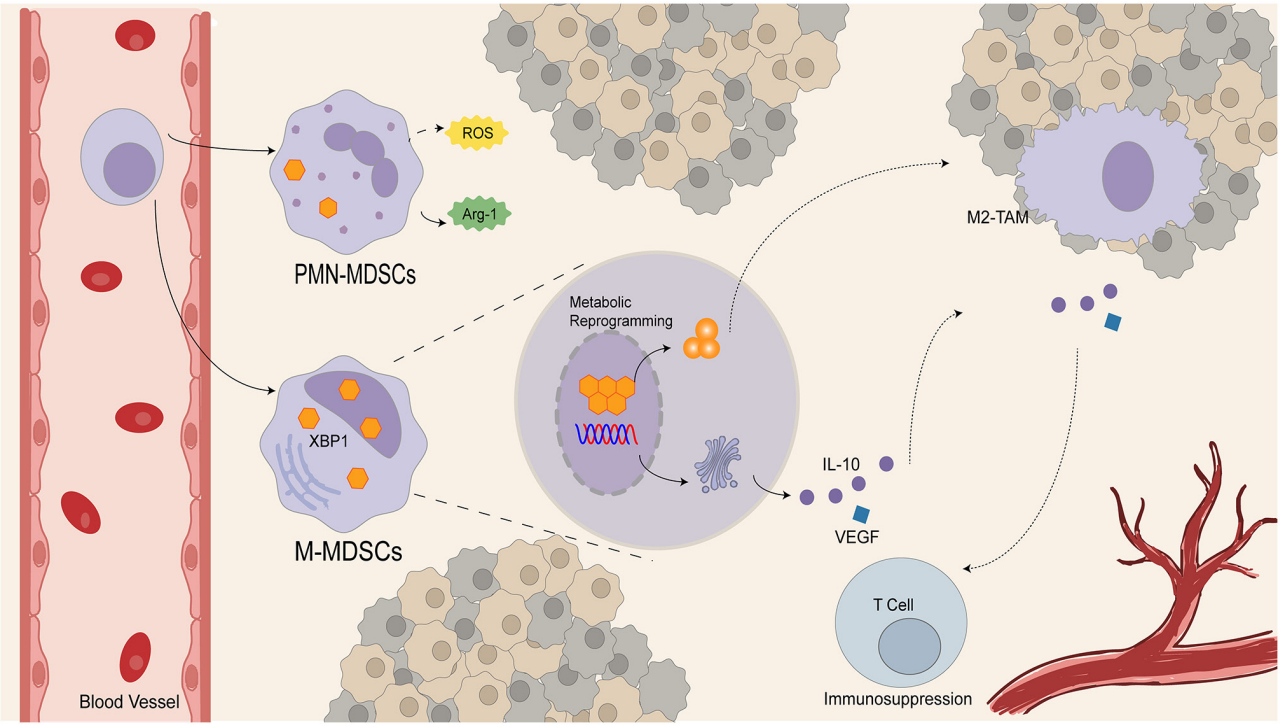

Figure 5. Heterogeneity and plasticity of MDSCs regulated by XBP1. PMN- and M-MDSCs exhibit distinct immunosuppressive profiles: PMN-MDSCs primarily produce ROS and Arg-1, while M-MDSCs undergo XBP1-driven metabolic reprogramming and differentiate into M2-TAMs, secreting IL-10 and VEGF. This plasticity enhances T cell suppression and supports tumor progression. Solid lines, directly validated in MDSCs; dashed lines, inferred from other cell types (macrophages, tumor and dendritic cells); dotted lines, hypothetical and requiring experimental validation in MDSCs. M-MDSC, monocytic myeloid-derived suppressor cell; XBP1, X-box binding protein 1; PMN, polymorphonuclear; ROS, reactive oxygen species; Arg-1, arginase-1; TAM, tumor-associated macrophage.

this subset, XBP1 activation serves as a critical driver of trans-differentiation. As XBP1 has been demonstrated to drive macrophage polarization toward the immunosuppressive M2 phenotype (77,135), it serves as a key transcriptional node that induces M-MDSCs to trans-differentiate into M2-like TAMs. This XBP1-mediated transition not only alters the cell phenotype but also establishes a long-term, stable immunosuppressive niche, shifting the reliance from acute suppressive mechanisms (such as ROS) to chronic paracrine suppression (such as IL-10 and TGF-β).

In summary, XBP1 shapes the myeloid landscape through a dual mechanism: Promoting the lipid-dependent survival and expansion of PMN-MDSCs, while simultaneously driving the trans-differentiation of M-MDSCs into M2-TAMs, thereby promoting tumor immune evasion (Fig. 5).

6. Therapeutic targeting of the XBP1 pathway: Pharmacological landscape, toxicity and combination with immune checkpoint blockade (ICB)

While targeting the IRE1α-XBP1 axis holds theoretical promise for counteracting MDSC-mediated immunosuppression, there are pharmacological, immunological and translational hurdles associated with systemic XBP1 inhibition.

Pharmacological landscape and delivery challenges. Current pharmacological interventions primarily focus on IRE1α, targeting either its kinase or endoribonuclease activity. Small molecule endoribonuclease inhibitors, such as STF-083010, 4μ8C and MKC-3946, have demonstrated preclinical efficacy in blocking XBP1 splicing and decreasing tumor burden (136-138). Specific kinase inhibitors have been developed to stabilize the IRE1α dimer in an inactive state, preventing both XBP1 splicing and regulated IRE1-dependent decay (RIDD) activity (139). However, these small molecules face delivery challenges, including poor aqueous solubility, rapid systemic clearance, off-target effects and limited penetration into the dense, fibrotic stroma of solid tumors (140). While emerging RNA nanotechnology platforms and lipid nanoparticle formulations offer strategies for the targeted delivery of XBP1 small interfering RNAs or inhibitors (141), achieving accumulation within the MDSC compartment without systemic off-target distribution remains a bioengineering hurdle.

Systemic toxicity and impact on normal myelopoiesis and DC function. The key barrier to systemic XBP1 inhibition is its indispensable role in normal immune homeostasis, particularly in myelopoiesis and DC function. XBP1 is required for the development, survival and antigen-cross-presentation capacity of conventional and plasmacytoid DCs (142). Global pharmacological inhibition or genetic deletion of XBP1 impairs DC maturation and markedly decreases the priming of tumor-specific $CD8^+$ T cells (143). Furthermore, the IRE1α/XBP1 pathway is essential for normal myelopoiesis in the bone marrow; its systemic blockade induces severe myelosuppression, neutropenia and unintended disruption of normal hematopoietic stem cell differentiation (13,144). Therefore,

while systemic XBP1 inhibition may eliminate immunosuppressive MDSCs, it simultaneously blocks the DCs and effector T cells required for a productive antitumor immune response. This paradoxical double-edged toxicity mandates the development of myeloid-specific or MDSC-targeted delivery systems to uncouple MDSC suppression from systemic immune impairment (19).

Combination with ICB: Preclinical success and clinical reality. Preclinically, combining IRE1α-XBP1 inhibitors with anti-PD-1 has shown potential. By alleviating MDSC-mediated exclusion and metabolic competition, XBP1 inhibition remodels the TME, increases T cell infiltration and overcomes primary or acquired resistance to ICB in murine models (104,109). To the best of our knowledge, there are no ongoing or completed phase I/II clinical trials evaluating the combination of specific IRE1α/XBP1 inhibitors with anti-PD-1 in human patients with cancer. The translation from murine to human efficacy is hindered by the aforementioned systemic toxicities (particularly DC impairment) and the lack of clinically viable, cell-targeted delivery vehicles. Future clinical applications depend on the successful development of localized or cell-specific targeted therapies that safely modulate the XBP1 axis in MDSCs without compromising systemic immune competence (Table V).

7. Context-dependent and paradoxical roles of the UPR in myeloid cells: Beyond immune suppression

While the present review focuses on how chronic ER stress and hyperactivated XBP1 in the TME drive MDSC-mediated immune evasion (13,120), the UPR in myeloid cells is not exclusively a detrimental or pro-tumorigenic mechanism (11). The biological consequences of ER stress and XBP1 activation are context-dependent, exhibiting paradoxical roles that range from promoting normal myeloid maturation to limiting hyper-inflammation (32,145). Recognizing this duality is key for a balanced academic perspective and safe design of future targeted therapies (146).

A distinction must be drawn between pathological, chronic and physiological, transient ER stress (11). Low-grade, transient activation of the IRE1α-XBP1 axis is required for normal myelopoiesis and the terminal differentiation of professional antigen-presenting cells. For example, XBP1 is key for the development, survival and functional maturation of conventional and plasmacytoid DCs (142). In these cells, moderate XBP1 activation drives the necessary expansion of the ER network to support high-capacity antigen processing and cross-presentation, thereby initiating productive antitumor $CD8^+$ T cell responses (143). Thus, while sustained XBP1 hyperactivation locks myeloid precursors into an immature, immunosuppressive MDSC state (13,120), physiological XBP1 signaling is the driver that allows these precursors to mature into immunostimulatory DCs (142).

The UPR serves as a critical 'inflammatory rheostat' that can actively limit hyper-inflammation and prevent tissue damage in myeloid cells (147). In acute infection or sterile inflammation, excessive activation of pattern recognition receptors overwhelms the ER, triggering the UPR (148). Rather than exacerbating inflammation, specific branches of the UPR exert anti-inflammatory effects (147). The endoribonuclease activity of IRE1α, for example, degrades specific pro-inflammatory mRNAs through the RIDD pathway, thereby acting as a negative feedback loop to prevent cytokine storms and macrophage hyperactivation (149). Furthermore, XBP1 has been shown to interact with and modulate other inflammatory cascades, such as the NLRP3 inflammasome and NF-κB pathways, dampening their overactivation to maintain cell and tissue homeostasis (150). In certain non-tumor inflammatory models, the conditional deletion of XBP1 in macrophages paradoxically exacerbates inflammatory responses and tissue injury, highlighting its physiological role in restraining excessive myeloid activation (145).

The impact of XBP1 on macrophage polarization is not universally polarized toward the pro-tumorigenic M2 phenotype (32,151). While the TME co-opts XBP1 to enforce M2-like TAM polarization, in other MDs, basal XBP1 activity is required to maintain the phagocytic and bactericidal functions of classically activated (M1-like) macrophages (145). The functional output of XBP1 is dictated by the intensity and duration of the stress signal, as well as by the surrounding cytokine and metabolic milieu (140).

In summary, the UPR in myeloid cells serves as a double-edged sword. The pathological hijacking of this pathway by the TME promotes immune escape, but its basal and transient activity is key for immune competence and inflammatory resolution. This paradox underscores the risks of systemic, long-term XBP1 inhibition in cancer therapy, which may induce immunodeficiency or trigger autoimmune hyper-inflammation. Future therapeutic paradigms must therefore aim to selectively uncouple the chronic, tumor-specific XBP1 signaling in MDSCs from the transient, physiological UPR required for normal myeloid homeostasis.

8. Bioinformatic evidence supporting the clinical relevance of the XBP1-MDSC axis

Preclinical studies have shown that XBP1 activation is associated with immunosuppressive features in the TME (13,120). However, translating these mechanistic findings from murine models to human clinical settings requires transcriptomic evaluation. To bridge this translational gap, bioinformatic analysis using public single-cell RNA (scRNA)-seq and bulk transcriptomic datasets was performed to support the preclinical hypotheses.

scRNA-seq analysis of human lung adenocarcinoma (LUAD) was conducted using the GSE146100 dataset (Fig. 6A-C) (152). The data were visualized and analyzed using Tumor Immune Single Cell Hub 2 (version 2.0; tisch.comp-genomics.org), which integrates comprehensive tumor scRNA-seq datasets with cell type annotation. Uniform manifold approximation and projection and violin plots confirmed the cell type-specific expression of XBP1, which was predominantly concentrated in monocyte and macrophage clusters within the human TME.

To evaluate the association between XBP1 expression and MDSC-related populations at the tissue level, Spearman rank correlation analysis was analyzed between XBP1 expression and immune cell infiltration across malignancies. Pan-cancer correlation heatmaps were generated using

Table V. Combination therapy strategies targeting the IRE1α/XBP1 pathway in the TME.

Combination strategy	Representative IRE1α/XBP1 inhibitors	Mechanism of action	Preclinical/clinical status	Challenges and limitations	(Refs.)
IRE1α inhibitors + ICB	STF-083010, 4μ8C, MKC-3946	Alleviates MDSC-mediated immunosuppression and metabolic competition; remodels the TME to enhance effector T cell infiltration; overcomes primary or acquired resistance to ICB	Preclinical. Combined efficacy demonstrated in murine models. No ongoing human clinical trials	Systemic XBP1 inhibition impairs normal dendritic cell maturation and antigen cross-presentation, potentially inhibiting T cell priming required for ICB efficacy	(104,109)
IRE1α inhibitors + chemotherapy/ radiotherapy	STF-083010, 4μ8C	Blocks survival signaling activated by treatment-induced ER stress; prevents the stress-mediated amplification and recruitment of MDSCs; sensitizes resistant tumor cells to apoptosis	Preclinical. Coordinated effects supported by *in vitro* and *in vivo* stress-response models	Chemo/radiotherapy induces ER stress; global IRE1α inhibition may exacerbate toxicity to normal rapidly dividing tissue (cardiotoxicity, vascular damage) and disrupt normal tissue homeostasis	(13,136-139,142-144)
IRE1α inhibitors + targeted immune/metabolic modulators	MKC-3946, STF-083010	Constructs a multi-target immune activation network; simultaneously blocks parallel immunosuppressive metabolic pathways (arginine depletion) driven by XBP1s	Preclinical. Lacks systematic *in vivo* validation for specific multi-target combinations in oncology	High complexity of multi-target pharmacokinetics; increased risk of overlapping systemic toxicity and unpredictable immune-associated adverse events	(140,141)
IRE1α inhibitors + targeted delivery systems	XBP1 siRNA, IRE1α-targeting nanomedicine	Enhances therapeutic specificity by selectively delivering inhibitors to the MDSC compartment; minimizes off-target systemic exposure	Early preclinical. Proof-of-concept for RNA nanotechnology exists, but MDSC-specific XBP1 formulations are in their infancy	Bioengineering hurdles in achieving precise accumulation within the dense, fibrotic stroma of solid tumors; potential immunogenicity of nanocarriers	(141)

IRE, inositol-requiring enzyme 1; XBP1, X-box binding protein 1; TME, tumor microenvironment; ICB, immune checkpoint blockade; MDSC, myeloid-derived suppressor cell; ER, endoplasmic reticulum; si, small interfering.

transcriptomic data from The Cancer Genome Atlas (TCGA) projects obtained from the Genomic Data Commons Data Portal (portal.gdc.cancer.gov/), including TCGA-skin cutaneous melanoma), TCGA-LUAD, TCGA-BRCA, TCGA-ovarian serous cystadenocarcinoma), TCGA-glioblastoma multiforme), TCGA-LIHC (liver hepatocellular carcinoma), TCGA-COAD (colon adenocarcinoma) and TCGA-STAD (stomach adenocarcinoma). The correlation analyses and visualizations were performed using Gene Expression Profiling Interactive Analysis (GEPIA)2 (gepia2.cancer-pku.cn) with Spearman rank correlation. XBP1 expression was positively correlated with the infiltration of neutrophils (used as a proxy

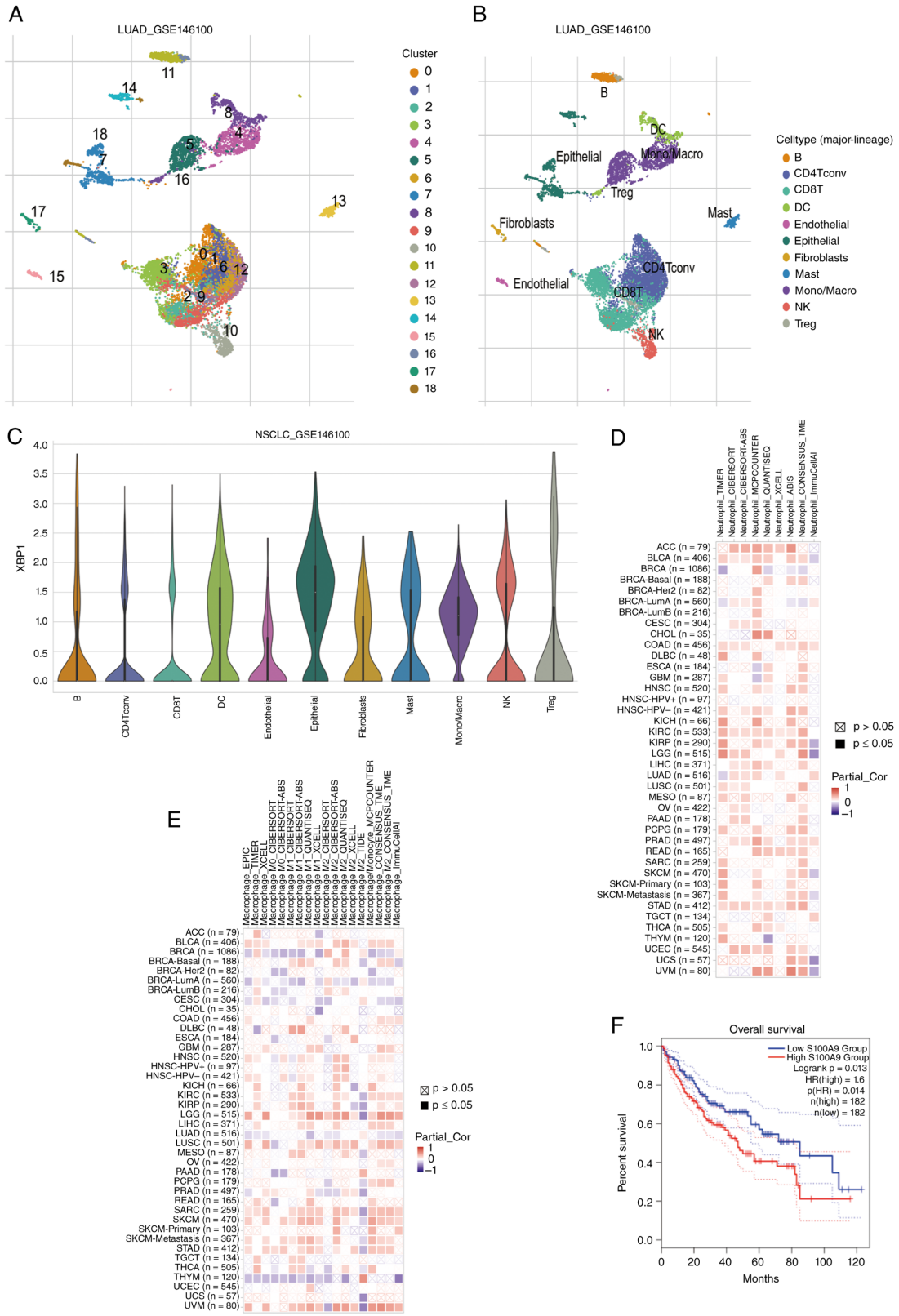

Figure 6. Bioinformatic validation of the XBP1-mediated immunosuppressive myeloid landscape and its clinical impact across human malignancies. (A) UMAP dimensionality reduction clustering of single-cell RNA sequencing data from human LUAD (accession no. GSE146100), illustrating distinct cellular clusters within the TME. (B) UMAP cell type annotation plot mapping the major lineages within the LUAD TME. (C) XBP1 expression levels across different annotated cell types, demonstrating its specific and significant enrichment in mono/macro populations. (D) Pan-cancer correlation heatmap depicting the partial cor between XBP1 expression and the infiltration abundance of neutrophils (serving as a transcriptomic proxy for PMN-MDSCs) across The Cancer Genome Atlas cancer cohorts. (E) Pan-cancer cor heatmap illustrating the positive cor between XBP1 expression and macrophage infiltration (representing M-MDSCs and TAMs) across human malignancies. (F) Kaplan-Meier survival curve demonstrating that high expression of the canonical MDSC marker S100A9 is significantly associated with poorer overall survival in patients with cancer. XBP1, X-box binding protein 1; UMAP, Uniform Manifold Approximation and Projection; LUAD, lung adenocarcinoma; TME, tumor microenvironment; mono, monocyte; macro, macrophage; cor, correlation; PMN, polymorphonuclear; M-MDSC, monocytic myeloid-derived suppressor cells; TAM, tumor-associated macrophage; HR, hazard ratio; CD4Tconv, conventional CD4+ T cells; NK, natural killer; DC, dendritic cell; Treg, regulatory T.

for PMN-MDSCs; Fig. 6D) (19) and macrophages (representing M-MDSCs and TAMs; Fig. 6E) (153). These findings are consistent with the hypothesis that tumors with elevated XBP1 signaling are associated with the presence or expansion of immunosuppressive myeloid subsets. Additionally, the TIMER2.0 web server (timer.cistrome.org/) was used to corroborate the correlation between XBP1 expression and immune infiltration levels. Consistent with the GEPIA2 findings, TIMER2.0 analysis revealed that XBP1 expression was positively correlated with neutrophil and macrophage infiltration across multiple TCGA cohorts, with Spearman correlation coefficients >0.30 and P-values below 0.05 in the GBM and SKCM cohorts (data shown in Fig. 6D and E).

Furthermore, the clinical prognostic impact of immunosuppressive myeloid accumulation was evaluated. Kaplan-Meier survival analysis for TCGA-SKCM cohort, performed using the 'Survival Analysis' module of GEPIA2 (version 2.0; gepia2.cancer-pku.cn/) (154), with a median cutoff and log-rank test, confirmed that high expression of S100A9, a canonical marker associated with MDSC abundance and function, was significantly associated with poorer overall survival (log-rank P=0.013; hazard ratio=1.6; Fig. 6F). Together, these bioinformatic findings offer transcriptomic evidence consistent with the preclinical hypothesis that XBP1 shapes an immunosuppressive myeloid landscape that may drive tumor progression.

Despite these supportive transcriptomic correlations, several important limitations should be acknowledged. First, the analyses are correlative in nature and do not establish causal associations between XBP1 expression, MDSC accumulation and clinical outcomes. Secondly, GEPIA2 and TIMER2.0 analyses are based on bulk tumor transcriptomes, which reflect the average expression across all cell types and may obscure cell type-specific signals. Third, these analyses measure total XBP1 mRNA levels rather than the active isoform XBP1s, which may be a more relevant biomarker of pathway activation. Fourth, the cancer type-specific variability in correlation strengths indicates that the XBP1-MDSC axis may operate differently across malignancies. Moreover, direct prospective clinical evidence evaluating dynamic XBP1 splicing and XBP1s protein activity as predictive biomarkers for patient response to immune checkpoint inhibitors remains limited (140). Consequently, the routine clinical utility of XBP1 as a predictive biomarker is still under investigation (140,155). Future research should prioritize the development of reliable, standardized detection methods for the XBP1s protein and prospectively evaluate its predictive value in well-designed clinical trials. This is key to bridge the gap between transcriptomic associations and clinical application.

9. Conclusion

The TME is a complex network involving survival pressures such as hypoxia, nutrient deficiency, accumulation of metabolic products such as lactate and enrichment of inflammatory factors. XBP1, a key stress response molecule, can sense ME stress signals and translate them into signals that regulate immune cell function homeostasis and reshape the local immune ME pattern of tumors through molecular regulation events.

Previous research focuses on the regulatory role of XBP1 in the metabolic processes and functional status of MDSCs, TAMs and other cells (13,36). This reveals the molecular mechanisms by which tumor cells manipulate the host immune system at the ecological regulatory level. Tumor cells do not passively escape immune system surveillance, but actively regulate the metabolic reprogramming process of myeloid immune suppressive cells through XBP1-mediated signaling pathways, regulate their functional phenotype transformation to enhance immune suppressive effects and thus construct a favorable TME for their survival and proliferation. Clarifying the regulatory mechanism of XBP1 on myeloid immune suppressive cells may provide experimental evidence to identify tumor treatment intervention targets and develop novel antitumor treatment strategies.

Future research should focus on detailed analysis of the complete molecular mechanism of the XBP1-mediated TME stress-immune regulation axis, including how XBP1 senses stress signals, downstream regulated target gene networks, interaction patterns with other signaling pathways and the common and specific characteristics of this axis in different types of tumor. In addition, intervention strategies targeting this pathway should be designed rationally, for example by developing inhibitors that specifically target XBP1 or constructing combination therapies targeting the XBP1 pathway with other immune regulatory pathways to achieve improved therapeutic efficacy. Additionally, natural compounds such as quercetin, known to modulate NLRP3 inflammasome activity (156), may represent adjunctive agents to mitigate inflammation-driven ER stress in the TME. These studies may transform the stress signal transduction mechanism that tumor cells rely on to maintain survival into a breakthrough point for therapeutic interventions. The aim is to block the immunosuppressive effects of XBP1 on myeloid immune suppressive cells through targeted intervention methods, while activating the antitumor immune system, relying on the role of the immune system to eradicate tumor cells. This may promote a new era centered on targeted metabolism and stress interaction networks, providing novel ideas and solutions to the present challenges faced by tumor immunotherapy, such as drug resistance and poor efficacy.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

ZC conceived the study, constructed figures and edited the manuscript. WL constructed figures and wrote and edited the manuscript. JT and GL edited the manuscript. JW, YZ and XC conceived the study and edited the manuscript. ZC and JW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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