Oxidative Stress in the Tumor Immune Microenvironment

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Abstract

Oxidative stress is one of defining features of the tumor microenvironment, which is closely related to the interactions between tumor cells and stromal cells. It affects tumor progression in many aspects. In the tumor microenvironment, primary immune cells have different functions, which together make up the immune defense line of the tumor. This review focuses on the relationship between oxidative stress and tumor-related immune system, specifically the effects and mechanisms of oxidative stress on different cell processes of immune cells in the tumor microenvironment. Then, we discuss the main overall effect of oxidative stress, immunosuppression, and its inspiration for tumor immunotherapy, which provides a theoretical basis for the feasibility of oxidative stress as a new target of tumor immunotherapy.

Keywords

Oxidative stress · Reactive oxygen species (ROS) · Tumor microenvironment · Immune cells · Immunosuppression · Immunotherapy

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2.1 Background

2.1.1 Oxidative Stress in the Tumor Microenvironment

In the process of cancer progression and metastasis, tumor microenvironment (TME) is a niche interacting with the host, which encompasses proliferative tumor cells, infiltrative immune cells, tumor matrix, and related vasculature, given that TME is regulated by tumor cells, in which various cells interact to form a complex environment, with characteristics of limited nutritional supply, hypoxia, pH deregulation, and oxidative stress (OS).

OS is a pathophysiological concept, which refers to a stress signal, reflecting that abundant reactive oxygen species (ROS) produced beyond eliminating oxidizing substance capacity in cells. It not only is a biochemical reaction but also has fundamentally complex cellular and molecular mechanisms, including membrane oxidation, mitochondrial metabolism, endoplasmic reticulum (ER) stress, DNA damage repair, gene transcription and expression, signal transmission, protein folding, and other cellular and molecular changes.

When cancer cell grows, malignant cells adapt to the surrounding matrix and undergo reprogramming, producing ROS and leading to OS status. It is recognized that endogenic or exogenous sources could cause OS in TME. Extrinsic: (1) Some components (such as neutrophils and macrophages) of TME can directly produce ROS. (2) Hypoxia can release the mitochondrial electron transport complex III or the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase to produce ROS. (3) OS, induced by microenvironment or senescence, results in senescent fibroblasts secreting senescent activated secretory pathway (SASP), which facilitates tumor growth through impacting on matrix and tumor cells. Intrinsic: Cancer cells downregulate JunD expression or increase COX-2, Nox-4, and Lox-5 activity to give rise to OS, thus aggravating the oxidative environment [1].

OS in TME has essential research significance. Mainly, the formation of superoxide, initiated by tumor necrosis factor α (TNF-α), platelet-derived growth factor (PDGF), interferon-γ (IFN-γ), transforming growth factor-β (TGF-β), interleukin-1 (IL-1), and epidermal growth factor (EGF), can induce the OS, which is associated with cancer and inflammation. Simultaneously, progressive tumors can induce significant OS and recruit inflammatory cells [2].

The effects of oxygen free radicals on oncology and carcinogenesis are multifaceted and remain unraveled. Herein, we mainly discuss the adverse intervention of OS against tumor immunity in TME. ROS, as soluble immunosuppressive factors, cause immune cell dysfunction in cancer patients [3]. In general, ROS affects proliferating signal regulation, tumor-invasive plasticity, tumor cell metabolism reprogramming, and gene mutation, which is closely related to tumor development [4]. Overall, the effects of OS on tumor progression include (1) the mutagenic potential of ROS, (2) the effect on regulating metabolic pathways to control proliferating and survival of cells, (3) the effect on cell movement and invasiveness, and (4) the effect of OS on stromal cells.

The exact nature of the effects of OS on cancer progression and therapeutic response needs further study. At present, advanced understandings of the processes and effects of OS-related networks are not fully elucidated, which hinders the implementation of new anticancer strategies based on OS.

2.1.2 The Major Tumor-Associated Immune Cells

Similarly, tumor immune microenvironment (TIME), encompassing tumor-infiltrating immune cells and factors, also engages in malignant cells progression and killing through interactions of components. Understanding relationships in TIME could address cancer immunotherapy through modulating various immune cell types.

Dendritic cells (DCs) are characterized as initiating immune reaction and tolerance toward specific antigen, termed antigen-presenting cells (APCs) [5]. Several studies have addressed that conventional DCs induce the antitumor immune response by means of capturing, processing, and then presenting tumor-associated antigens (TAAs) via major histocompatibility complex (MHC) molecules [6]. Concomitantly, soluble and costimulatory factors are secreted by DCs owing to shaping T cell activity. Naïve T cells could also recognize TAAs, cross-presented from DCs, which endows $CD4^+$ T cell antitumor capacity as well as $CD8^+$ T cell cytotoxicity competence [7, 8]. Furthermore, tumor-derived DNA triggers activation of DCs and IFNs production via cyclic GMP-AMP synthase (cGAS), stimulator of interferon genes complex (STING), and interferon regulatory factor 3 (IRF3) pathway in anti-TME [9].

T cells work as a pivotal force in antitumor immunoreaction, which can be divided into regulatory T cells (Tregs) and effector T cells (Teffs), encompassing $CD4^+$ helper T (Th) cells as well as $CD8^+$ cytotoxic T lymphocytes (CTLs) cells. CTLs work as fundamentally effector cells toward tumor damage, while Th cells are necessary for helping CTL-dependent tumor eradication. Firstly, CTLs scan tumor cells to find counterpart peptide-MHC (pMHC) complexes followed by integrin engagement, and migration of T cell slows down [10, 11]. Subsequently, target cells are employed by CTLs and induced killing [12, 13]. Notice that C-X-C motif ligand (CXCL12), a kind of chemokine, could weaken CTL function by restraining migration into the tumor in pancreatic ductal adenocarcinoma in contrast to IL-12 that promotes CTL effector function via facilitating the formation of CTL synapse [14, 15]. Moreover, Th cells could also induce antitumor responses in TME, such as co-stimulation, antigen presentation, and T cell homing [16]. Partial Th cells express tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), perforin, granzymes, or death meditator Fas ligand (FasL) to kill tumor cells, while others exhibit indirect function via enhancing CTL immune responses [17, 18].

Previous studies suggest that Treg-mediating immunosuppression contributes to tumor immune evasion [19]. Moreover, cell-cell contact and soluble factors have been considered as possible suppressive mechanisms [20]. Tregs are capable of crippling antitumor immune cell function, through interacting with DCs, Teffs, and

NK cells, respectively [19–24]. Besides, Tregs, expressing programmed cell death protein 1 (PD-1), obtain intensely immunosuppressive activity by enhancing T cell receptor (TCR) as well as signal of CD28 in the treatment of PD-1 blockade [25].

As significant humoral immune participant, tumor-infiltrating B cells (TIBs) function as killing tumor cells through expressing granzyme B and TRAIL in TME [26]. Nevertheless, B cells also exert antitumor suppression in TME. At first, the tumor-targeted antibody could produce circulating immune complexes (CICs) in tumor tissue, which initiates the complement pathway to promote cancer development [27]. Second, B cells secret pro-tumorigenic factors, such as lymphotoxin. Furthermore, regulatory B cells (Bregs) suppress antitumor immunity via secreting anti-inflammation cytokine, IL-10 [28]. Bregs also induce M2 macrophage polarization and Treg production through secreting TGF-β [29, 30]. Based on the dual roles of B cells in TME, it is necessary to formulate a reasonable patient stratification strategy for B cell-related treatment and take different treatment measures for patients with different tumor-related B cell typing results [31].

Natural killer (NK) cells are characterized as mediating effective cell killing and immunosurveillance in TME. The NK cell activation and inhibition depend on the integrating signals produced by inhibitory and activating NK receptors (iNKRs and aNKRs) and the dynamic balance [32, 33]. Changing of surface markers, for instance, lacking human leukocyte antigen class I molecules and upregulated damage-associated proteins, is required in NK cell recognition and killing in TME [34]. Subsequently, NK cells exert cytotoxicity capacity, depending on producing perforin and granzymes in granules and relying on death receptors, to induce apoptosis [35, 36]. Besides, activated NK cells express cytokines and chemokines, such as IFN-γ and CCL3, to induce indirect killing. Some studies demonstrated that NK cells with memory properties acquired a longer survival time and better cytotoxicity toward tumor cells after the second stimulus [37].

Monocyte/macrophages are pivotal lymphocytes in innate immune responses, the functions of which could be affected by the surrounding microenvironment. Pro-inflammatory cytokines, ROS/RNS, and other cytotoxic mediators are produced by M1 macrophages. Functionally, activated M2 macrophages protect tissue from chronic inflammatory microenvironment through generating a small quantity of IL-12 in contrast to a high amount of IL-10 [38]. In TME, tumor-associated macrophages (TAMs) exhibit IL-12^{low}/IL-10^{high}/TGF-β^{high} phenotype like M2 macrophages, which impedes T cell proliferation and cytotoxicity and initiates Tregs [39, 40]. Besides, chemokines, cytokines, ROS, and proteolytic enzymes are also secreted by TAMs to promote tumor progress [39]. TAMs could digest the extracellular matrix (ECM) to promote tumor metastasis. More importantly, due to growth factors and anti-inflammatory cytokines in TME, differentiated M1 macrophages can be “re-educated” to M2 macrophages [39]. Therefore, utilizing the feature of “re-polarization” to convert M2 into M1 macrophages could be a potential strategy for tumor treatment.

2.2 OS and Tumor-Associated Immune Cells

2.2.1 The Effects of OS on Teffs in TME

It has been generally found that cancer-related T cells (T cells refer to Teffs here, if not specified) have low reactivity and impaired function. Based on previous studies, the increase of OS in TME is the leading cause of T cell depletion induced by the tumor cells. The effects of OS on T cells are multifaceted. At present, the studies focus on the consequences of OS, and the mechanism involves multiple pathways, which is complex and needs further research. T cells affected by OS are characterized by activated T cells being more susceptible to OS compared with primary T cells [41]. $CD8^+$ T cells, in particular, are susceptible to apoptosis induced by oxygen free radicals [42]. Besides, different doses of OS have different effects on T cells. ROS can participate in signal transduction and gene expression of T cells as a signal molecule. Incubation of T cells with low-level hydrogen peroxide can promote the activation of NF-κB, induce the expression of IL-2, and stimulate cell proliferation. In contrast to activation, the addition of hydrogen peroxide inhibited cell proliferation to a large extent.

Maintaining the level of redox inside and outside the cell is the premise of T lymphocyte's normal function. Due to various factors, TME becomes a chronic oxidative environment, which has a significant impact on T lymphocytes. OS is an important factor in determining the activation, differentiation, apoptosis, proliferation, and function of T cells. We will discuss the specific effects and central mechanisms of OS on T cells below (Fig. 2.1).

2.2.1.1 T Cell Function

The OS caused by excessive ROS in TME weakened the effect of T cells on tumor resistance, mainly leading to T cell hyporesponsiveness [43]. TCR signaling pathway is vital to T cell activation. Several TCR signaling molecules have been known to be affected by OS, such as the downregulation of p56lck, TCR ζ, and linker of activated T cells (LAT) [44]. In TCR signaling pathway, TCR-induced intracellular signal that originated from tyrosine phosphorylation in ITAM sequence of CD3 molecule and phospholipase C-γ1 (PLC-γ1) was activated through phosphorylation and then mediated the opening of subsequent Ca^{2+} channel and Ca^{2+} influx, and increased intracellular Ca^{2+} concentration catalyzed the regulation of downstream gene expression by related transcription factors [45].

Effects on TCR Signaling Pathway

The molecular mechanism of OS-induced hyporesponsiveness of T cell is achieved by targeting specific molecules in the TCR signaling mechanism. PLC-γ1-dependent tyrosine phosphorylation defect and calcium mobilization damage can cause T cell hyporesponsiveness. Compared with healthy T cells, the pattern of tyrosine phosphorylation protein in low-reactive T cells changed. In the low-reactive T cells, ROS targeted inhibition of PLC-γ1, resulting in TCR connection no longer inducing PLC-γ1 activation, PLC-γ1-dependent tyrosine phosphorylation defect, and Ca^{2+}

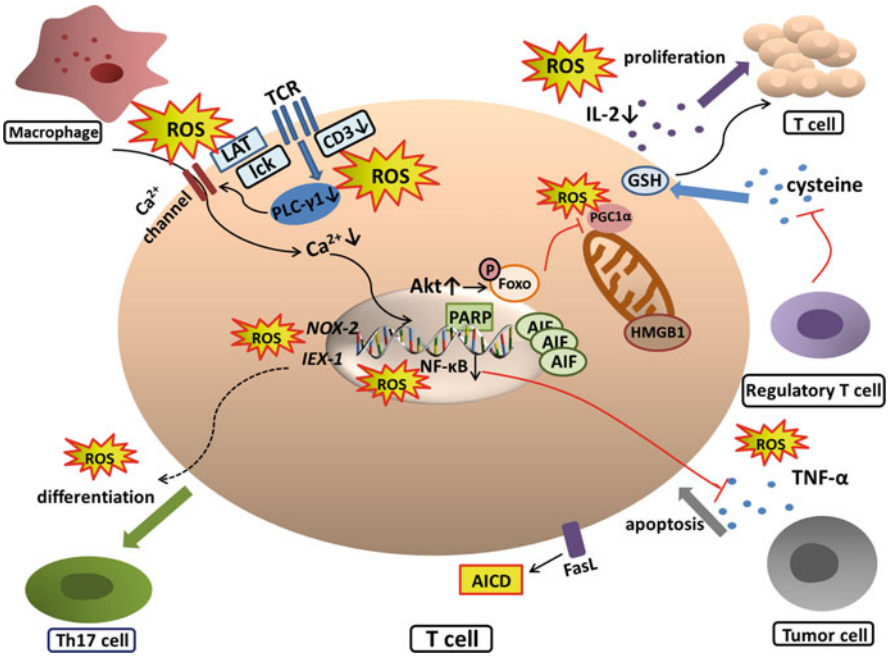

Fig. 2.1 The main effects and central mechanisms of OS on T cells in TME. The molecular mechanism of OS-related T cell hyporesponsiveness can be induced by influencing various components of TCR signaling mechanisms. PGC1α can be a crucial mechanism link between Akt and the inhibited oxidative metabolism of tumor-infiltrating T cells, which impair mitochondrial-related functions of T cells. The ROS-related gene *NOX-2* and *IEX-1* may play a role in Th17 cell differentiation. OS can induce the death of tumor-host T cells through NF-κB-TNF-α interaction. ROS can trigger PARP and apoptosis-inducing factor (AIF)-dependent cell death of T cell. OS can affect proliferation by affecting the production of IL-2 in T cells. Tregs can participate in OS-induced T cell proliferation inhibition in TME through impairing the synthesis of GSH in T cell

flux reduction, that is, downstream TCR signal pathway block [46]. Besides, ROS targets key TCR signal molecules, which have different effects on their structure and stability. The expression of p56lck, TCR ζ, and LAT key TCR near-end signal molecules in low-reactive T cells was impaired. The C-terminus of TCR ζ and the proximal domain of the p56lck membrane were oxidized by ROS, leading to the alteration of protein structure and the impairment of TCR function. The specific manifestations are selective loss of signal molecules in low-reactive T cells, ROS-dependent rapid degradation of p56lck, main structural changes and edge degradation of TCR ζ, and loss of LAT signal. The deterioration of the proteasome is a secondary effect leading to low reactivity [44]. TCR-CD3 complex of T cells in tumor patients showed a structural abnormality, especially the disappearance of the CD3ζ chain [47]. It then results in T cell response inhibition, which is antigen-specific. Studies showed that OS mediates CD3ζ decreasing in the interaction between tumor macrophages and T cells [48]. The OS of tumor-bearing mouse

macrophages (TBM-mØs) may lead to the inhibition of the exchange of CD3ζ and newly synthesized CD3ζ on the surface [48].

Effects on Mitochondrial-Related Functions

Oxidative metabolism is the key medium for T cells to exert their functions, and mitochondrial regulation of oxidative metabolism and other functions of T cells are very critical, such as the increase of cytokine production in T cells whose mitochondrial activity is high [49]. PGC1α is a node of multiple cross-linking signal pathways, which can directly interact with Foxo3a to regulate the expression of OS protection genes to control OS response [50]. It also controls mitochondrial biogenesis. PGC1α can be used as the transcription coactivator in the process of mitochondrial replication, and it can be regulated by Akt signaling pathway. Specifically, Foxo family transcription factors can promote the expression of PGC1α [50], while Akt signaling can phosphorylate and deactivate Foxo to play the role of oxidative metabolism inhibition. Continuous and progressive mitochondrial function and quantity loss of tumor-infiltrating T cells have been found, which are caused by the increase of Akt activation, and subsequently cause inhibition of transcription of Foxo-programmed PGC1α. It was demonstrated that PGC1α could link the Akt signaling pathway and the inhibited oxidative metabolism condition of T cells in TME. Moreover, inhibitors of Akt may have immunomodulatory effects, and Akt-targeted therapy may provide new ideas for tumor immunotherapy [51].

2.2.1.2 T Cell Differentiation

In tumor-bearing hosts, OS can cause T cells to tend to polarize to Th2 phenotype [42] and regulate Th1 and Th2 cytokines to varying degrees. These changes of cytokine profile are significant in the process of tumor formation because Th1 cytokine has the antitumor immune function, and the priority transfer to a Th2 profile facilitates tumor progression. This transition from Th1 type to Th2 type also contributes to the reduction of CTL activity [52]. NOX-2 is a ROS-producing enzyme gene. The study showed that in the cells lacking NOX-2 emerged the decrease of IL-4 and the increase of IL-17 production so that the NOX complex may affect Th17 cell differentiation [43]. Besides, the rise of ROS formation in mitochondria after T cell activation can mediate the process of gene IEX-1 deletion, promoting Th17 cell differentiation in early response [53].

2.2.1.3 T Cell Death

NF-κB-Related T Cell Death

NF-κB plays a crucial role in host immunity and lymphoid organ development [54]. NF-κB was downregulated in tumor-bearing mice, indicating that OS inhibited NF-κB [55]. NF-κB can suppress TNF-α expression [56]. In the process of tumor development, if the activity of NF-κB is disturbed, it causes T cell apoptosis induced by TNF-α [57]. On the one hand, TNF-α secreted by the tumor cells has a deadly effect on thymus T cells [58]. It plays a variety of biological activities by activating signal pathways (including IKK, JNK, and caspases) and regulating immune response, inflammation, and apoptosis. On the other hand, ROS itself is a critical

factor in TNF-α-induced apoptosis. In T cells, long-term exposure to OS can inhibit the activity of NF-κB translocating into the nucleus [59]. The disorder of NF-κB subcellular distribution induces T cell apoptosis mediated by TNF-α and causes thymus atrophy through activation of TRADD-related caspase-8. The inhibition of NF-κB mediated by ROS and enhancement of TNF-α levels can synergistically lead to T cell death [57]. Moreover, NF-κB can mediate in T cell activation-induced cell death (AICD). The expression of FasL is also closely related to AICD. ROS promotes NF-κB, which increases FasL expression, and then mediates T cell apoptosis. Vitamin E can inhibit the activity of NF-κB, through its function of eliminating free radicals, resulting in FasL expression blockade and T cell AICD development [60, 61].

Oxygen-Free Radicals Induce PARP-Dependent Death of Cytotoxic T Cells
Poly (ADP-ribose) polymerase (PARP), a nick sensor enzyme [62] activated by DNA single-strand breaks, is an essential target in cancer. It was pointed out that phagocyte-derived ROS triggered PARP and apoptosis-inducing factor (AIF)-dependent cell death of cytotoxic T cell. It is accompanied by the decrease of mitochondrial transmembrane potential, AIF nuclear accumulation, and large-scale DNA fragmentation [63].

In addition, OS can regulate the transport of high mobility group box 1 (HMGB1) transport and activity [43]. In the process of T cell apoptosis, mitochondrial ROS oxidation releases HMGB1 in the process of cell apoptosis. HMGB1 can also regulate T cell immune response [64].

2.2.1.4 T Cell Proliferation

The Depletion of GSH in Cells Significantly Inhibited the Proliferation of Lymphocytes to Mitotic Lectin
Glutathione (GSH), as an indicator of OS, is an important intracellular antioxidant. Intracellular GSH level is an essential factor in regulating the redox environment of T cells by interacting with APCs [2]. The results show that the proliferation of lymphocytes to mitosis is directly dependent on the effectiveness of GSH, and limiting the amount of GSH available in cells could inhibit lymphocytes growing during activation [65]. The consumption of GSH in T cells can hamper IL-2 production. IL-2 can stimulate T cell proliferation, and IL-2 secretion regulated by redox regulation is essential in T cell proliferation [66]. Thus, OS can affect the production of IL-2 and thus impair T cell proliferation.

Tregs Participate in OS-Induced T Cell Proliferation Inhibition in TME
In addition to TCR signaling pathway, costimulatory signaling, and related cytokines, the proliferation of T cells also needs a suitable redox microenvironment formed by APCs. Tregs can reshape this environment through a variety of strategies and further inhibit the proliferation of Teffs. On the one hand, Tregs can mediate redox state disturbance and interfere with GSH metabolism of DC and Teffs [67]. On the other hand, cysteine is necessary for T cells for synthesizing GSH, which

provides reduction capacity for synthesis of DNA and cell cycle ([68, 69]). T cells mostly rely on cysteine from DCs to metabolize normally. Tregs can inhibit the accumulation of extracellular cysteine through the competitive mechanism. The signal pathway linking Tregs to redox metabolism may help identify potential new therapeutic targets.

It should be noted that OS not only affects the effect of infiltrating T cells; the T cells in the primary immune chamber can also be affected. For example, the decrease of monocytes in circulation and the spleen, thymic atrophy, and myelosuppression were observed in mice with advanced ascites cancer [57, 70]. Further investigation will help study the role of OS in tumor-induced T cell inhibition. Still, the critical details of the relationship among OS, inflammatory mediators, and T cell function in TME need further study. T cell therapy can combine with ROS scavenger, which can lead to the enhancement of antitumor T cell function, thus improving therapeutic effects [43].

2.2.2 The Effects of OS on NK Cells in TME

The functions of NK cells are increasingly appreciated owing to tumor cell killing without previous sensitization. In TME, various tumor cells and tumor-related cells could produce factors, such as IL-10, IL-6, and TGF-β, which can functionally impair NK cells [71]. As an essential antitumor cell, NK cell cytotoxicity and other functions are strongly suppressed by ROS in TME (Fig. 2.2) [72]. Studies unraveled that immunosuppressive milieu induces NK cell into apoptotic states and losing responses toward activating signals [63, 73].

ROS Activate PARP-Dependent NK Cell Apoptosis
PARP functions as a nick sensor enzyme and signaling molecule. PARP-1 is the majority type of PARP, which could be activated by damaged DNA, OS, and signals in cytoplasmic membrane receptors. In TME, human acute myeloid leukemia (AML) cells generate extracellular ROS by NADPH oxidase complex; thus, PARP-1-dependent apoptosis is initiated in adjacent NK cells [74]. Firstly, overactivated PARP-1 conveys the death signal to mitochondria, and mitochondrial transmembrane undergoes depolarization. Then, high-conductance porosity occurs, and mitochondria release AIF, which is transferred to NK cell nucleus, triggering fragmentation of chromatin into large fragments (50 kbp) [63, 75]. In the downstream of PARP activation, caspases are activated and could modify the fragmentation of DNA. Activating the caspase enzyme system results in partial secondary internucleosomal fragmentation from large fragments into shorter fragments [63].

Therefore, PARP-based immunotherapy is promising in cancer and inflammatory pathologies [76]. Olaparib, a PARP inhibitor, increases the NK killing capacity in breast cancer, non-small-cell lung carcinoma, and chordoma [77]. Moreover, inhibiting ROS production could also be a potential strategy. Studies revealed that

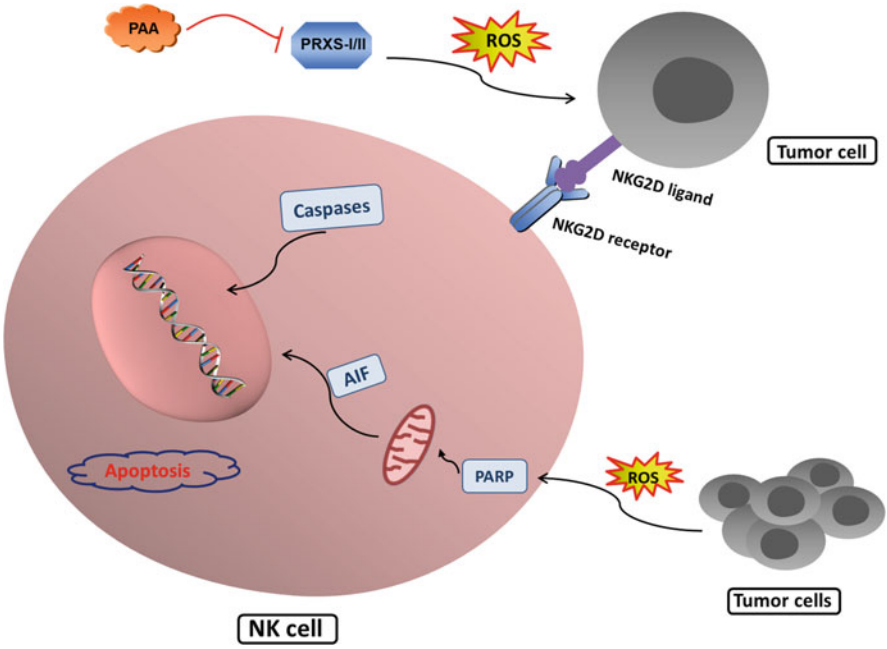

Fig. 2.2 The main effects and central mechanisms of OS on NK cells in TME. ROS impacts on NK cell function and destiny in TME: Tumor cells produce ROS, which results in NK cell PARP activation. Accordingly, mitochondria release AIF, entering cell nucleus. Furthermore, caspases are activated. Then, genomic DNA is degraded into short fragments, and NK cell undergoes apoptosis. New findings demonstrate that parvifoline AA could inhibit peroxiredoxins I/II function, resulting in ROS/ERK production and NKG2D ligands highly expressing in tumor cell. Therefore, NK cell could interact with tumor cells via NKG2D receptors efficiently; thus, NK cell exhibits tumor cell killing

jointly using NADPH oxidase inhibitor histamine dihydrochloride and cytokine IL-2 increases French-American-British M4/M5 AML patients' survival [74]. Besides, destroying the DNA repair system in tumor cells by controlling PARP could enhance chemotherapy and radiotherapy effect due to DNA damaging [78].

However, studies demonstrated that parvifoline AA (PAA) could help tumor killing by NK cells via increasing ROS. PAA is proved to inhibit peroxiredoxins I/II (PrxI/II) function. Accordingly, ROS/ERK was activated, resulting in NK group 2 member D (NKG2D) ligands highly expressing on hepatocellular carcinoma (HCC) cells. Subsequently, NK cells with NKG2D receptors could recognize HCC cells and induce cytotoxicity. Hence, PrxI/II is a potential immunotherapeutic target, and PAA is a promising agent toward HCC treatment [79].

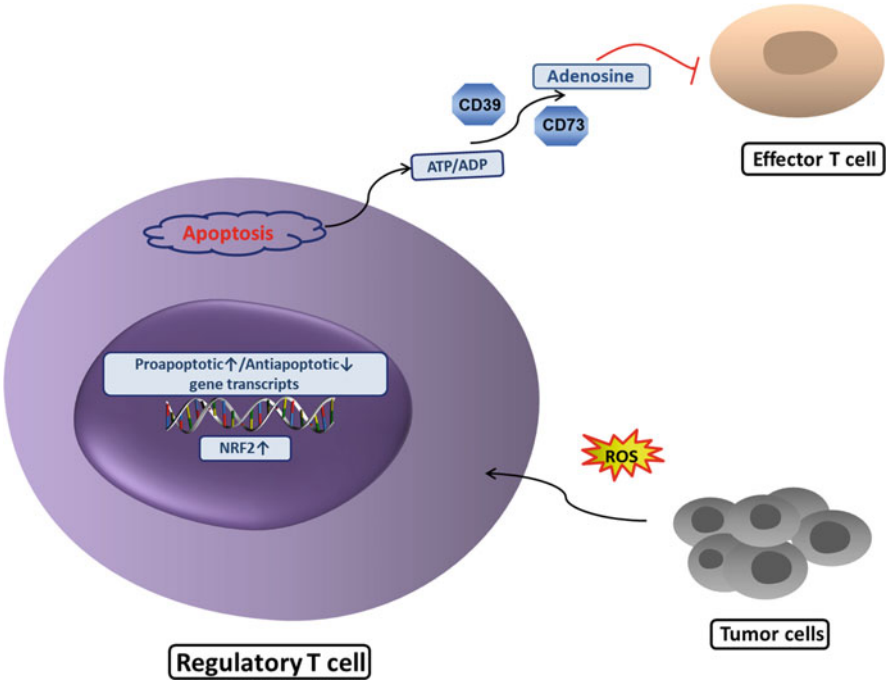

Fig. 2.3 The main effects and central mechanisms of OS on regulatory T cells in TME. ROS impacts on regulatory T cell (Treg) function and destiny in tumor microenvironment: Tumor cells produce ROS, leading to NRF2 and proapoptotic gene transcripts upregulation while antiapoptotic gene transcripts downregulation in Tregs. Then, Tregs endure apoptosis. Furthermore, apoptotic Tregs release ATP/ADP, which convert into adenosine, inhibiting effector T cell function in antitumor responses

2.2.3 The Effects of OS on Tregs in TME

OS has a significant impact on the metabolic behaviors of Tregs (Fig. 2.3). Previous studies demonstrated that Tregs undergo apoptosis in TME, which led to efficient antitumor suppression.

Tregs Endure Apoptosis

In TME, studies have found that vulnerable NRF2-associated antioxidant system resulted in Tregs apoptosis [80, 81]. Transcription factor NRF2 and its relevant genes are controlled by the antioxidative system. In murine and human ovarian-cancer-infiltrating Tregs, the expressions of NRF2, heme oxygenase, and other antioxidant proteins are reduced. As a consequence, Tregs are sensitive to ROS challenge, and high expression of proapoptotic genes and low expression of antiapoptotic genes are detected. Besides, mitochondrial activity is increased in Tregs [81].

Tregs Suppress Teffs by Adenosine
A high level of ATP/ADP is released from apoptotic Tregs and transformed into immunosuppressing adenosine [82]. The relevant energy metabolism, purine metabolism, and pyrimidine metabolism genes are highly expressed [83]. Therefore, apoptotic Tregs not only generate a large number of ATP to self-provide but also release from pannexin-1-dependent channels to the adjacent environment [84]. Subsequently, apoptotic Tregs express ectoenzymes CD39 and CD73 to metabolize ATP to adenosine and suppress Teffs through A_{2A} receptors, which recognize adenosine and induce IL-2 suppression on Teffs [81].

Tregs Promote Immunosuppression
Human ovarian-cancer-infiltrating apoptotic Tregs inhibit the generation of IL-2, TNF, and IFN-γ in Teffs. Moreover, Tregs abolish natural and induced PD-L1 checkpoint blockade Teff antitumor immunity in MC38 colon cancer. Thus, compared with live Tregs, apoptotic Tregs promote tumor growth by suppressing TAA-specific Teffs and inhibiting the expression of cytokines in Teffs more efficiently [81]

In summary, OS enhances the apoptosis of Tregs in TME. Different from Teffs, Tregs are not sensitive to glycolytic restriction but vulnerable to ROS, which leads to antitumor immunosuppression. These studies implied that removing the treatment effect of PD-L1 blockade and undergoing apoptosis in Tregs were novel mechanisms of tumor immune escape.

2.2.4 The Effects of OS on B Cells in TME

It has been demonstrated that the presence and function of B cells play an essential role in tumor prognosis. However, studies about the effects of OS on B cells in TME are relatively few. In immune cells, ROS, as the second messenger, participates in the cell response and function of B cells [85]. ROS can regulate the maturation, activation, proliferation, apoptosis, and function execution of B cells.

There are many investigations on B cell apoptosis among the possible death modes. In the study of chronic lymphocytic leukemia, through the cascade response of cytochrome c and caspases, ROS can cause B cell apoptosis [86]. Besides, ROS can also activate caspase-9, leading to the improvement of X-linked inhibitor of apoptosis-associated factor 1 (XAF1) and follow-up B cell apoptosis. ROS-activated JNK/p38 MAPK signaling pathway can also induce B cell apoptosis, mainly leading to Bax transfer into mitochondria. Then, mitochondrial membrane potential is damaged; caspase-9 and caspase-3 are activated [64]. Thus, OS is a critical inducing factor of B cell apoptosis (Fig. 2.4).

Studies about the ROS in B cell precursor acute lymphoblastic leukemia demonstrated that ROS could contribute to the genetic instability in B cells, which is characterized by double-strand breaks [87]. Besides, no other researches show the influence of ROS in the antitumor immune response of B cells. However, ROS plays

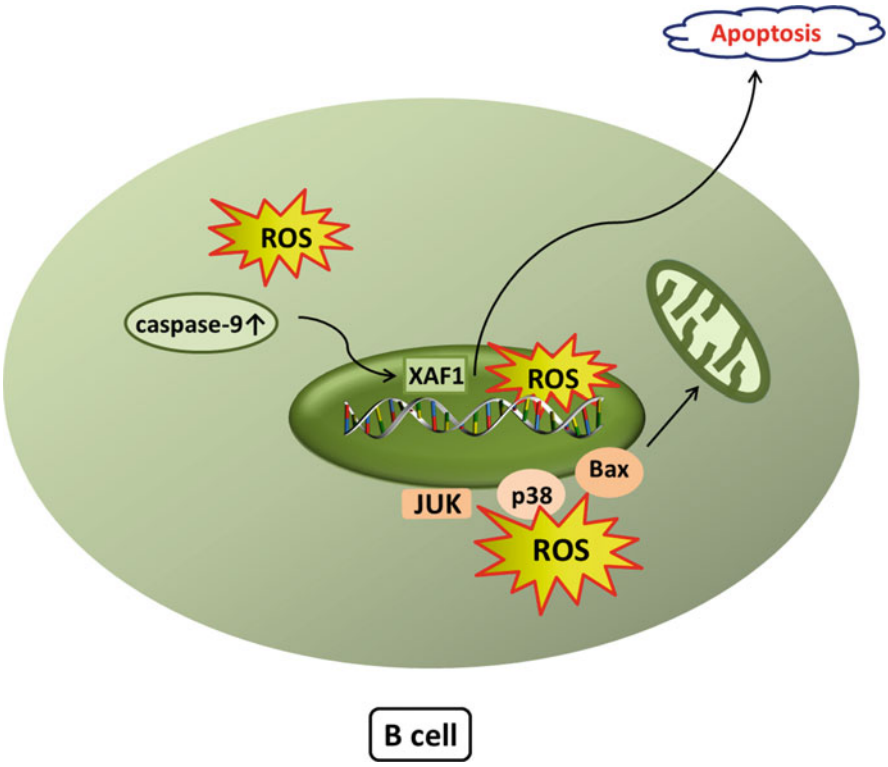

Fig. 2.4 The main effects and central mechanisms of OS on B cells in TME. ROS can activate caspase-9 to increase X-linked inhibitor of apoptosis-associated factor 1 (XAF1) and induce the apoptosis of B cells. JNK/p38 MAPK signal pathway activated by ROS can also cause the apoptosis of B cells, which leads to the translocation of Bax into mitochondria, the destruction of mitochondrial membrane potential, and the activation of caspase-9 and caspase-3. ROS increases the genetic instability and double-strand break of B cells in antitumor immune response

a crucial role in B cell function and its specific subpopulation differentiation, so we can consider that ROS is vital in tumor immune response mediated by B cells [88].

Combined with the above discussion of the dual role of tumor-infiltrating B cells during immune regulation and the specific impact of OS on it, the effects of OS on B cells on tumor immune regulation and the overall process of diseases are also dual. At present, there is no direct study on the effects of OS on B cells in TME. Due to the instability of ROS, its impact on the formation of B cell subsets is not apparent, including regulatory B cell and tumor-related B cell subsets functions. More roles of ROS in B cells are still to be found.

2.2.5 The Effects of OS on DCs in TME

DCs are characterized as specialized APCs. However, intracellular ROS can disrupt tumor-associated DCs (tDCs) lipid metabolism and capacity of antigen presentation, leading to antitumor suppression in human and murine ovarian cancer (Fig. 2.5) [89].

XBP1 Induces ER Chaperone Expression

The ER processes transmembrane and secretory proteins through glycosylation, folding, and disulfide bond formation. High levels of ROS, hypoxia, and acidosis can impair ER function in protein maturation [90]. When aberrant proteins accumulated, "ER stress" or unfolded protein response (UPR) happens, aiming at recovering the metabolic balance of ER. Simultaneously, the activated signal path of UPR engages in increasingly producing ROS through impacting on mitochondrial functions [91]. The sensors of UPR are ATF6, PERK, and IRE1α, which are localized at ER membrane [92]. Among these UPR arms, IRE1α is most conserved.

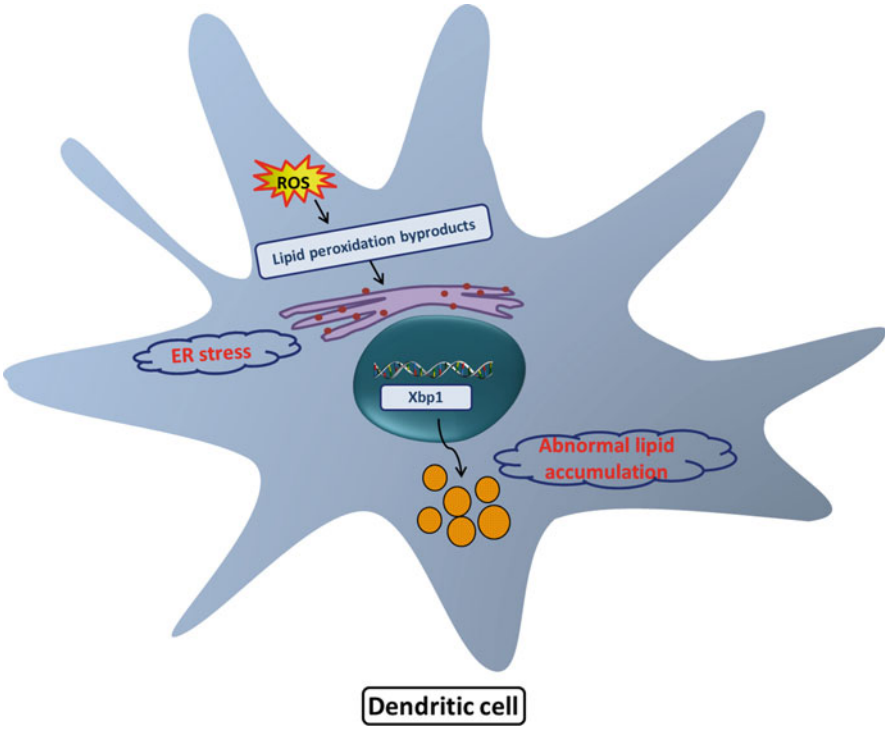

Fig. 2.5 The main effects and central mechanisms of OS on dendritic cells in TME. ROS impacts on dendritic cell (DC) function and destiny in tumor microenvironment: ROS leads to generation of lipid peroxidation byproducts; then, ER stress occurs. Accordingly, transcription factor Xbp1 is produced and facilitates abnormal lipid accumulation. Finally, the lipid metabolic balance is broken, and antitumor immunity capacity is hampered in DCs

The kinase domain oligomerizes and autophosphorylates in ER stress process, and 26 nucleotides are removed from the unspliced *X-box binding protein 1* (*Xbp1)* mRNA due to the activated RNase domain, and then *Xbp1* is produced, which encodes transcription factor XBP1 initiating ER chaperone expression ([89, 93]).

ROS Induces ER Stress
In TME, ROS generates lipid peroxidation byproducts, resulting in ER stress and XBP1 activation in tDCs [94]. Moreover, XBP1 promotes lipid accumulation via Agpat6, Fasn, Scd2, and Lpar1, to regulate triglyceride biosynthetic [89]. Apart from 4-HNE, there are some lipid peroxidation byproducts, including acrolein, malondialdehyde, and 4-hydroxyhexenal, that could lead to antitumor suppression via ER stress [95]. Overall, the production of 4-HNE and other lipid peroxidation byproducts caused by ROS makes IRE1α-XBP1 arm overactivated, which destroys lipid metabolism balance in tDCs. Accordingly, the antitumor immunity of T cells is inhibited.

Studies elucidated that targeting IREIα-XBP1 axis could be a new strategy in immunotherapy. Using IRE1α inhibitors could improve anticancer immunity and tumor cell death. Silencing XBP1 by siRNA-encapsulating nanocarriers renders tDCs acquiring immunocompetence to support ovarian-cancer-infiltrating T cells [89].

2.2.6 OS and Macrophages in TME

2.2.6.1 OS Effect of TAMs

A point to be discussed in this review: unlike the relationship between other immune cells and OS conditions in TME, in macrophages, most studies discuss the mechanisms by which they cause OS states in the TME. TAMs infiltration in TME is related mainly to the poor prognosis of cancer, which can mediate a variety of tumor-promoting phenomena: inflammation, vascular regeneration, and OS.

Macrophages are widely recruited in a variety of tumors, and their functions are various: directly produce ROS/RNS, and secrete pro-inflammatory cytokines that promote matrix reaction, both of which can affect the redox state of TME [96]. TAM-induced chronic inflammatory response produces ROS, which plays a vital role in activating the transcription factors that are sensitive to redox conditions and are involved in all processes of tumor development. Therefore, TAMs can promote tumor growth mainly by its contribution to the OS state in TME. They participate in the tumor-promoting physiological effects of downstream immunosuppression, cell proliferation, angiogenesis, and tumor metastasis.

In most tumors, the tumorigenic effect of TAMs is dominant. For example, it has been shown that TAM-regulated OS is the primary process that affects the C26 colon cancer cell proliferation. Through the activity of NADPH oxidase in macrophages, it maintains the physiological range of OS and angiogenesis in the C26 colon cancer environment. It promotes the production of tumor angiogenic proteins [97]. In

conclusion, TAMs are one of the main factors in the formation of OS state in the microenvironment, which promotes epithelial-mesenchymal cell transition (EMT), aggressiveness, and the diffusion of metastatic cells [96].

2.2.6.2 The Effect of OS on Macrophages

The Polarization of Macrophages

Reprogramming TAM from the M2 phenotype to M1 is associated with OS in TME and cancer cells, which promotes tumor killing. The switch of TAM polarization from M1 to M2 is parallel to the progressive inhibition of NF-κB in tumor progression [98]. There are studies about mitochondrial Lon that can be induced by OS. The results showed that in TME, the expression of Lon in macrophages and cancer cells increased, which could induce the production of ROS-p38-NF-κB-dependent cytokines, and M2 macrophage polarization was driven by IL-6, IL-13, IL-4, and VEGF-A. The overexpression of Lon induced p38 expression, and p38-NF-κB signal transduction dependent on ROS induces the specific inflammatory cytokines and thus drives the polarization of M2 macrophages [99]. Studies showed that macrophage polarization is related to taking in $KRAS^{G12D}$ protein released from cancer cells that suffer from ferroptosis. ROS can induce cancer cells to release $KRAS^{G12D}$ during OS, and $KRAS^{G12D}$ is packaged into exosomes. After it is absorbed by macrophages through advanced glycosylation end product-specific receptor (AGER)-dependent mechanism, it can promote macrophage polarization through activation of fatty acid oxidation dependent on STAT3. Specifically, in macrophages, $KRAS^{G12D}$ activates STAT3 through AGER, leading to selective upregulation of CPT1A and ACADM. This is conducive to M2 polarization of macrophages and fatty acid oxidation [100].

Phagocytosis

It showed that excessive ROS exposure could lead to the impairment of macrophage function, such as phagocytosis. This macrophage dysfunction is partly due to the oxidation of mannose-binding lectin, and it is necessary for the process of active phagocytosis [101]. Moreover, a new study reveals the role of ROS in macrophage function from a new perspective. CLEC10A is a human sugar receptor expressed in macrophages. CLEC10A on macrophages can mediate the uptake of damaged cells during antigen presentation; CLEC10A ligands (CLEC10AL) exist in human tumor tissues. The increase of ROS induces the expression of CLEC10AL in breast cancer cells. Mechanistically, it is proved by the elevated expression of GalNAc transferase 6 (GalNT6) and GalNT2, and GalNT6 was translocated from cis-Golgi to trans-Golgi compartment. The changes in molecular mechanisms caused by ROS lead to the buildup of truncated glycans on the surface of cells, and they lead to the enhancement of phagocytosis of macrophages [102]. The positive expression of macrophage CLEC10A has been proved to be related to the improvement of prognosis in breast cancer patients (Fig. 2.6).

Overall, the relationship between macrophages and OS has not been comprehensively discussed in cancer. Combined with the interaction between OS and

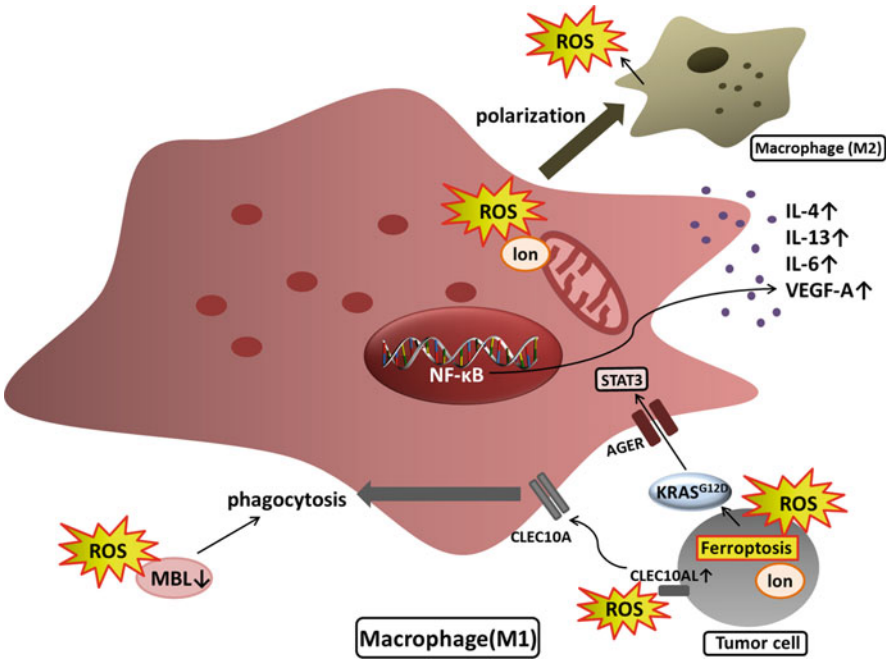

Fig. 2.6 The main effects and central mechanisms of OS on macrophages in TME. The overexpression of Lon triggers ROS-dependent p38, and p38-NF-κB signal transduction induces expression of inflammatory cytokines and thus drives the polarization of M2 macrophages. ROS-induced $KRAS^{G12D}$ releasing from cancer cells during oxidative stress is packaged into exosomes and absorbed by macrophages through AGER-dependent mechanism and then promotes macrophage polarization through STAT3-dependent activation of fatty acid oxidation. The dysfunction of phagocytosis is partly due to the oxidation of the key component necessary for active phagocytosis, mannose-binding lectin (MBL). ROS can also improve the phagocytosis indirectly by inducing the expression of CLEC10AL on the tumor cell surface

macrophages, the effect of OS on the overall process of the tumor is complicated. Therefore, it is imperative to find the right balance in OS-related therapy [98].

2.3 The Significance of OS on TIME

From the above discussion, we can see that the effects of OS on different immune cells are multifaceted. Here, we focus on the information about OS and tumor immunosuppression. Cancer immunosurveillance can be regarded as an inflammatory process, which is vital in the recognition and elimination of early tumors by the immune system. Immunosuppressive TME promotes tumor deterioration. ROS may be the immunosuppressive participants; that is, the impaired immune response of cancer patients is related to OS.

There have been a lot of therapeutic researches based on the role of ROS in tumor cells, such as killing tumor cells by stimulating the increase of ROS production. Besides, a therapeutic strategy targeting TME has been proposed to improve their sensitivity to immune monitoring. There is no study combining OS-related therapy with targeted immunotherapy [4]. However, some studies have shown the crosstalk relationship between OS and tumor immunotherapy. For example, tumor checkpoint inhibitors as immunomodulators can reduce tumor burden by regulating tumor OS. Studies have shown that the response of mice with colorectal cancer to immunotherapy and chemotherapy resistance of ovarian cancer patients can also be mediated by OS [103].

Collectively, recognizing and targeted enhancing the keyway of the antitumor immune response, maintaining a certain level of ROS in tumor cells, and TME can improve the prognosis and the survival of cancer patients.

2.3.1 OS and Immunosuppression in TME

Immunosuppression in tumor development refers to that under the condition of cancer, the immune dysfunction of tumor patients may cause tumor immune escape. The main features of low immune system function are weakened response to antigens, decreased T cell proliferation, decreased signal transduction, and impairment of transcription factor activity in important lymphocytes [55].

ER Stress

The deficient microenvironment of the tumor, such as hypoxia, acidity, and OS, can increase the intracellular ROS content and mediate the ER stress of cells. The function of some immune cells in TME can be regulated by ER stress and further hinder the antitumor immunity. Specifically, ER stress has two tasks for tumor-related immune regulation: one is to mediate the immunosuppression of immune cells through tumor-cell-releasing factors under ER stress; the other is to directly generate ER stress in immune cells, mainly involving myeloid cells (neutrophils, MDSCs, and macrophages), with different mechanisms. For example, the production of 4-HNE and other lipid peroxidation byproducts caused by ROS in DCs makes IRE1a-XBP1 overactivated, which destroys their lipid metabolism balance, impends the antigen presentation of T cells, and thus hinders protective immune response development [104].

Therefore, targeting ER stress could also serve to improve the clinical tumor immune efficacy [104]. Studies demonstrated that silencing of XBP1 in DCs might prolong host survival by siRNA-encapsulating nanocarriers. Then, the antitumor suppression is reversed, and antitumor immune responses are initiated. Targeting XBP1 resulting from ER stress in tDCs provides us a novel therapeutic method [19].

Mitochondrial OS

Apart from the effect of driving the polarization of M2 macrophages, the OS of mitochondria induced by Lon can also promote the metastasis behavior of the tumor and change the cytokine balance in TME to establish immunosuppression. Specifically, cancer cells with high expression of Lon release specific cytokines, which activate the upregulation of endogenous Lon in macrophages and promote macrophages to secrete cytokines supporting tumor. The inflammatory cytokines secreted by cancer cells and macrophages induced by mitochondrial Lon-ROS circulate in the TME, promoting EMT/the plasticity of cancer, angiogenesis, and M2 macrophage polarization, thus triggering immune escape and tumor metastasis [99]. Therefore, regulating the redox balance of mitochondria in specific cells in TME may be a strategy of tumor immunotherapy to improve T cell function [99].

ROS, as an Inflammatory Mediator

ROS, as an inflammatory mediator in TME, is able to inhibit the function of immune cells directly. For example, OS can upregulate IL-8 and TNF in DCs. Additionally, the ROS of MDSCs plays an important role. MDSCs often appear in the TME with OS characteristics, and the ROS production of MDSCs is upregulated after being activated in cancer, while the ROS derived from MDSCs can impair cellular immune response. Important lymphocytes are all the targets of ROS. ROS regulates the metabolism of MDSCs. ROS can maintain the undifferentiated state of MDSCs and exert immunosuppression. The increase of endogenous H_2O_2 levels may be one of the mechanisms of tumor preventing MDSCs from differentiation. HIF-1 and NRF2 participate in the regulation of pathways of MDSCs. Targeted reduction of ROS in MDSCs can enhance the effect of tumor immunotherapy [105].

Therefore, antioxidant programs have been introduced into tumor treatment and prevention. However, the role of ROS in tumor progression is still controversial. Due to its high cytotoxicity, ROS can be used to kill tumor cells. Therefore, the key task of individualized immunotherapy is to identify the inflammatory characteristics of cancer patients and find the balance of ROS-related treatment [106].

Based on the impact of OS on primary tumor-related immune cells, the global immunosuppression consequences are produced. Understanding the molecular events of OS-induced immune cell inactivation may help determine the treatment strategies to alleviate cancer-related immunosuppression.

Taking T cells as an example, OS affects their survival, proliferation, activation, differentiation, and other physiological functions. OS disrupts T cell-mediated immune function, which is one of the crucial reasons for tumor development. The inhibition of T cell response leads to the immunosuppression of the tumor-bearing state. Considering the mechanism of ROS-mediated immunosuppression, it is important to use antioxidants to regulate the reaction of antitumor T cells [43].

In the study of Tregs, OS-mediated apoptotic Tregs can eliminate the anti-PD-L1-mediated antitumor effects, emphasizing that the oxidation pathway can be used as a checkpoint in metabolic process to control Tregs' behavior, which can affect the effect of cancer checkpoint therapy. Thus, the impact of OS on tumor immune cells

may be related to the mechanism of immune escape and checkpoint drug resistance [81].

Besides, some immune cells are associated with the formation of OS conditions in TME, that is, the ROS level released by activated macrophages or granulocytes infiltrated by tumor increases, which may become an obstacle for active immunotherapy of cancer. It suggests that in addition to the therapeutic idea of regulating OS to improve the activity of immune cells, targeting tumor immune cells to improve the OS environment specifically is also vital.

2.3.2 Inspiration for Clinical Treatment

All researches above provide a new idea for tumor immunotherapy. The immunotherapy of solid tumors mainly includes the following ways: activating the functions of tumor-associated lymphocytes, enhancing phagocytosis of tumor-related macrophages, targeting inhibition of MDSCs and Tregs, and regulatory therapy of TME. It focuses on the direct enhancement of tumor-related immune cell function or the regulation of microenvironment. Our review provides a theoretical basis for the combination of OS regulation of TME and immune cell function regulation.

According to the above, OS may widely impair the survival and normal function of primary tumor-related immune cells, and treatment aimed at reversing immunosuppression may need to focus on the change of redox state in cancer patients. TME regulation therapy is mediated by interfering with the main feature of tissue hypoxia, OS, metabolic disorder, and chronic inflammation of TME. It can improve the internal environment, provide appropriate environmental signals for the normal physiological activities including the activation and proliferation of killer immune cells, and improve the immune environment by providing a variety of immune regulatory factors [107]. For example, hypoxia can disrupt oxygen metabolism, resulting in a large amount of ROS, making the TME in OS state. It can be restored by adjusting abnormal tumor blood vessels, which can alleviate local hypoxia and promote the function of effector immune cells [107].

Besides, some studies have proposed some drugs that mediate the recovery of immune cell function through OS. It is possible to improve the prognosis of tumor patients by the treatment that can correctly intervene in the OS condition of TME through processes such as improving the T cell-mediated antitumor effects. Traditional Chinese medicine may be used in the treatment of TME regulation [107]. As a component of traditional Chinese medicine, flavonoids are potent antioxidants, which can resist the local OS of tumor cells [108]. Curcumin, as an antioxidant, is used as an antineoplastic drug, which can reduce the systemic toxicity, neutralize the OS in the immune system, and protect the function of T cells. Specifically, it can interfere with the fate of T cells in TME by mediating NF-κB-ROS-TNF-α, neutralize tumor-induced OS, restore the NF-B activity of T cells, inhibit TNF-α, and thus reduce tumor-induced T cell apoptosis [57]. Besides, it can also play a role in Th cell polarization, such as normalizing Th1 cytokine profile, preventing Th2 polarization, and mediating Treg accumulation [109]. All-trans-retinoic acid (ATRA) is a mature

promoter of human MDSCs, thus reversing its immunosuppressive function. Specifically, ATRA promotes the accumulation of GSH in MDSCs, which leads to a decreased ROS level, and prevents MDSCs from differentiating into mature myeloid cells [110]. Antioxidant therapy can block the differentiation of TAMs and the occurrence of tumors [111]. For example, caffeic acid (CA) can enhance the cytotoxicity of M1 macrophages and inhibit tumor growth, and its antioxidant activity can mediate the inhibition of TAMs [112]. Specifically, CA can increase the functional capacity of macrophages, which causes an increase in the level of pro-inflammatory cytokines, such as IL-2, IFN-γ, and IL-12, and increase the tumor-killing activity of macrophages. These antitumor treatment measures will cause metabolic changes of TME, thus affecting the function of immune cells [113].

Collectively, immunotherapy and TME regulation should be paid more attention to in the new treatment strategies of cancer patients. Targeted treatment strategies should be designed for different types of immune cells so that they can regulate the innate immune system of the tumor efficiently and establish systematic antitumor immunity. Besides, the use of environmental regulation drugs such as antioxidants can improve TME, restore immune cell function, and prevent tumor growth. Finally, we should pay attention to the combination of universality and individualized therapy.

2.4 Summary and Perspectives

The characteristics of the main effects of OS on tumor-related immune cells can be summarized as multiple aspects and consequences, most of which cause immunosuppression. Among them, the researches on T cells (especially Teffs) and NK cells are more mature, while the existing studies on B cells and macrophages are less. OS is one of the most critical factors that cause the low reactivity of Teffs in the tumor. It mainly affects the TCR signal pathway and causes death, proliferation, and differentiation inhibition of Teffs. The dysfunction of Teffs in TME seriously affects the effectiveness of tumor immune regulation, which leads to the acceleration of tumor progression. In addition to Teffs, NK cells can also kill tumor cells. Under the influence of OS, apoptosis mediated by PARP and AIF occurs. Therefore, PARP can also be used as a potential therapeutic target for tumor and inflammatory pathology. The apoptosis of Tregs in TME is caused by OS and even promotes the tumor immunosuppression, which is a new mechanism of tumor immune escape. Different from T cells, the role of B cells in tumor immunity is less elucidated. Excessive ROS may cause gene instability and double-strand break of B cells or induce apoptosis of B cells in TME. As a typical critical APC, in DCs, intracellular ROS can affect the metabolism and antigen-presenting ability of tumor-related macrophages, mainly through ER stress effects and lipid peroxidation. Finally, unlike other cells, macrophages are an important source of OS in TME, which is the leading cause of the tumorigenic effect of TAMs. Besides, OS can mediate the influence of cell polarization. Macrophages have M1 and M2 types. M1 type mainly plays an inhibitory role in cancer, while M2 type plays a different position. OS can help its

polarization to M2 direction. Besides, excessive ROS exposure can lead to macrophage dysfunction.

According to a series of researches, we focus on the consequences of immunosuppression. Tumor immunosuppression is a phenomenon of immune escape caused by the decline of related immune system function in the process of the tumor. Many studies clearly show that many immune cell biological phenomena related to OS, such as ER stress, mitochondrial OS, and ROS as inflammatory mediators, are closely related to tumor immunosuppression. The overall consequences of OS on specific important tumor-related immune cells suggest that we can improve the activity of related immune cells by regulating the level of OS in TME.

Therefore, many related clinical therapies for OS are derived from interfering with the malignant characteristics of TME and improving the conditions for immune cells. Traditional Chinese medicine mediates TME reconstruction, especially the use of antioxidants to improve the immune cell damage caused by OS, such as curcumin. At the same time, we should also pay attention to the rational use of antioxidants. Considering the effect of OS on tumor progression, a high concentration of ROS in cells mediates the death of tumor cells. Still, it may jeopardize tumor immunity, thus increasing the severity of the tumor. Therefore, we should focus on the balance of oxidative regulation in the OS-related treatment of tumors and pay attention to the analysis of the individualized immune status of tumor patients for targeted therapy.

In conclusion, ROS in OS can be used as one of the immunosuppressive factors, which can lead to immune cell dysfunction in tumor patients. OS can mediate the overall downregulation of antitumor immunity. However, the current researches mainly focus on the research results of the operating system, and the relevant mechanisms need to be further studied. These findings provide new targets for tumor immunotherapy and new ideas for clinical treatment.

Conflict of Interest Authors declare no conflict of interest.

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