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Review

Targeting HMGB1 in the Treatment of Non-Small Cell Lung Adenocarcinoma

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Simple Summary: Lung cancer is the most commonly diagnosed cancer in the world, and with recent success of immunotherapy for cancer treatment, there is hope that a functional cure for lung cancer is within our grasp. However, many patients with lung cancer continue to have low response rates to immunotherapy such as immune checkpoint inhibitors. Innate immune proteins like High Mobility Group Box 1 (HMGB1) may be key to improving the effect of immune-based cancer treatment for patients that currently do not respond to therapy. This review outlines ways to target HMGB1 in order to alter the immune response across several in vivo and in vitro models.

Abstract: Evidence of immunogenic cell death as a predictor of response to cancer therapy has increased interest in the high molecular group box 1 protein (HMGB1). HMGB1 is a nuclear protein associated with chromatin organization and DNA damage repair. HMGB1 is also a damage-associated molecular pattern (DAMP) protein and promotes proinflammatory signaling in a paracrine and autocrine manner. Extracellular HMGB1 can promote activation of NF-kB and is associated with several chronic inflammatory and autoimmune diseases, including sepsis, rheumatoid arthritis, atherosclerosis, chronic kidney disease, systemic lupus erythematosus (SLE), as well as cancer. In this review, we describe studies that demonstrate the use of deacetylase inhibitors and HMGB1 inhibitors to alter the expression and localization of HMGB1 in cancer cells, with a focus on lung cancer. The drugs described herein are well established and frequently used in human and small mammal studies. The main objective of this review is to summarize the potential benefit of targeting posttranslational modification of HMGB1 to decrease inflammatory signaling in the tumor microenvironment, and perhaps lead to improved response to current immunotherapeutic approaches.

Keywords: cancer; immunotherapy; HMGB1; lung cancer; inflammation

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1. Introduction

Lung cancer is the most common form of malignancy worldwide and is the leading cause of cancer-related deaths in both men and women. Like many cancers, lung cancer is particularly lethal as a result of its ability to effectively camouflage itself from the immune system, leading to late diagnosis and poor response to treatment [1,2]. This allows the uncontrolled growth of cancer cells and the establishment of an immunosuppressed microenvironment. The uncontrolled growth and local immunosuppression are associated with increases in metastatic growth and the development of tumors distal from the primary site [3]. Current treatment methods are heavily reliant on cytotoxic chemotherapies that target the rapidly growing cells that have dysfunctional DNA repair mechanisms. Molecular targeted therapy is a promising new therapeutic technique involving the interference of

integral molecules in cancer growth and metastasis. These therapies often involve very little threat to the host in comparison to more traditional treatment methods and have demonstrated remarkable clinical success in the treatment of many cancer types including breast, leukemia, colorectal, lung, and ovarian cancers [4]. Novel targeted therapeutics with less toxicity have the potential to increase overall survival and radically change the quality-of-life of patients. The more recent advances in immunotherapies such as tumor cell-based vaccines, chimeric antigen T cells, and immune checkpoint inhibitors have increased the hope that less toxic therapies will become the norm [5]. In lung cancer for instance, the use of immune checkpoint inhibitors increases the survival rate of previously treated cancer patients from 5 to 16% [6]. However, there are many patients who do not benefit from these approaches at present, either due to cost, low expression of checkpoint molecules, or poor response to treatment. Therefore, improving our understanding of the immune response within the tumor microenvironment is likely to allow more patients to benefit from this new technology and perhaps improve the prognosis of patients that, despite our best efforts, could not be successfully treated in the past.

Within the tumor microenvironment, innate immune proteins reside that are capable of skewing the adaptive immune response in favor of either proinflammatory or anti-inflammatory responses [7]. The elimination of neoplasms typically occurs following recruitment of cytotoxic immune cells elicited by pro-inflammatory cytokines like IL-1, IL-6, and TNF alpha [8–10]. However, the immune response is not a simple on/off mechanism especially in the context of cancer. Some innate immune molecules known as damage associated molecular pattern (DAMPs) initiate pro-inflammatory signaling, which recruit tumor infiltrating immune cells [11]. However this does not always result in the clearance of harmful cells or pathogens. In some instances, the immune response is suppressed by the expression of specific DAMPs [12]. One DAMP, high mobility group box 1 protein (HMGB1), has been shown to have both an activating and suppressive effect on the immune response [13–15]

HMGB1 is a non-histone chromatin packing protein that resides within the nucleus [16,17]. Under stress, HMGB1 dissociates from chromatin and relocates to the extracellular space [18,19]. Outside of the cell, HMGB1 is able to act as a ligand for a variety of receptors and stimulates recruitment of lymphocytes [13,20–22]. Understanding how HMGB1 expression regulates immunomodulation is an active area of research. Consequently, HMGB1 has been shown to be a major contributor to many inflammatory diseases [23–25], and its release can be altered by administering natural compounds and inhibition of deacetylases [26–29]. Increasing evidence suggests that HMGB1 has influence on the immune state within tumors [14,15,30], which makes controlling HMGB1 localization in cancer cells a potential immunomodulatory target that could be used to induce anti-tumor cytotoxic lymphocyte activity. Herein, we systematically reviewed the literature for studies that utilize deacetylase and HMGB1 inhibitors to target HMGB1 in lung cancer and other select models of cancer and lung disease.

2. Materials and Methods

A medical librarian created the literature search strategy after meeting with a member of the research team to clarify goals and further define selection criteria. The search strategy was built in Ovid MEDLINE using Medical subject headings and keywords to describe the following concepts: HMGB1 inhibitors or HDAC inhibitors and cancers. The search was then translated to three other databases: EMBASE, Cochrane Library, and Scopus. Databases were chosen to be inclusive of international medical literature. Searches were run without limits from database inception through 29 April 2020. After deduplication, 490 titles and abstracts were uploaded to Rayyan [31] for independent review by two researchers. Following the title and abstract review, PDFs of 69 selected studies were uploaded for full-text screening and independently reviewed by two researchers (Figure 1).

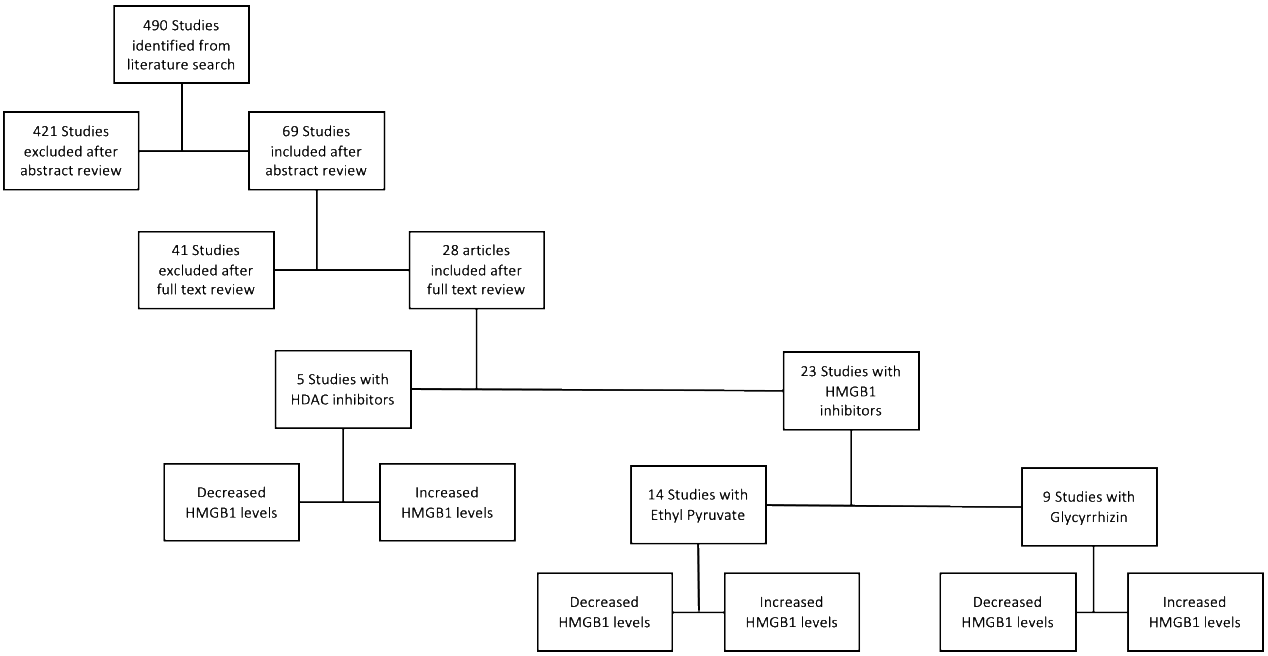

Figure 1. Schematic of data extraction from research studies included.

Studies were included if they met the following criteria: (1) The model systems described human patients with lung cancer, human cancer cell lines, or animal models of lung cancer or lung disease/injury; (2) Drugs were either HDAC inhibitors or HMGB1 inhibitors (glycyrrhizin or ethyl pyruvate); (3) Study was published in a full-text article. Studies were excluded if (1) they described animal models of cancers or diseases in organs other than the lung; (2) they were only reported in an abstract, poster, or conference presentation, etc. Twenty-nine studies met the criteria and were included in our analysis. Data was extracted from each study independently by two authors using a custom data extraction form that collected data on the following outcomes: HMGB1 gene and protein expression, extracellular HMGB1 protein level, five-year overall survival, and change in tumor size. Using the extracted data, summary statistical tables and figures were created using major themes of the model, drug used, HMGB1's cellular retention, HMGB1's release, tumor size, and survival (Table 1). This review is based on these major themes.

Table 1. Targeting of HMGB1 in lung cancer and other disease models.

Study No.	Authors and Year	Study Model	HMGB1 Inhibitor (Class)	Intracellular HMGB1	Extracellular HMGB1	Tumor Size	Survival
1	Buoncervello et al. 2012 [32]	human breast cancer cells	Apicidin (HDAC inhibitor)	↑	↑	N/A	↓
2	Booth et al. 2017 [33]	human melanoma cells	AR42 (HDAC inhibitor)	N/A	↑	N/A	N/A
3	Xia et al. 2016 [34]	human cervical cancer cells	Ethyl Pyruvate (anti-inflammatory)	↑	↓	N/A	N/A
4	Li et al. 2012 [35]	human gallbladder cancer cells	Ethyl Pyruvate (anti-inflammatory)	↓	N/A	N/A	N/A
7	Yan et al. 2012 [36]	human liver cancer cells	Ethyl Pyruvate (anti-inflammatory)	no change	↓	N/A	N/A
8	Cheng et al. 2014 [37]	human liver cancer cells	Ethyl Pyruvate (anti-inflammatory)	↓	N/A	↓	N/A
9	Lim et al. 2007 [38]	human lung cancer cells (glucose-deprivation)	Ethyl Pyruvate (anti-inflammatory)	↑	↓	N/A	N/A
10	Wang et al. 2012 [39]	human lung cancer cells	Ethyl Pyruvate (anti-inflammatory)	N/A	↓	N/A	N/A
11	Liu et al. 2019 [40]	human lung cancer cells	Ethyl Pyruvate (anti-inflammatory)	↓	N/A	N/A	N/A
12	Yang et al. 2015 [41]	human pancreatic cancer (presence of TRAIL)	Ethyl Pyruvate (anti-inflammatory)	N/A	↓	N/A	N/A
13	Relja et al. 2018 [42]	mouse lung injury	Ethyl Pyruvate (anti-inflammatory)	↓	N/A	N/A	N/A
14	Shang et al. 2009 [43]	mouse lung injury	Ethyl Pyruvate (anti-inflammatory)	N/A	↓	N/A	↑
15	Luan et al. 2013 [44]	rat lung injury	Ethyl Pyruvate (anti-inflammatory)	↓	N/A	N/A	N/A
16	Tang et al. 2010 [45]	human pancreatic cancer	Ethyl Pyruvate/Glycyrrhizin (HMGB1 inhibitor)	N/A	↓	N/A	N/A
17	Alexander et al. 2019 [46]	human keratinocytes	Glycyrrhizin (HMGB1 inhibitor)	N/A	N/A	↓	N/A
18	Gui et al. 2020 [47]	human lung cancer and epithelial cells	Glycyrrhizin (HMGB1 inhibitor)	N/A	↓	N/A	N/A
20	Chen et al. 2017 [48]	human nasal polyps	Glycyrrhizin (HMGB1 inhibitor)	↑	↓	N/A	N/A

Table 1. *Cont.*

Study No.	Authors and Year	Study Model	HMGB1 Inhibitor (Class)	Intracellular HMGB1	Extracellular HMGB1	Tumor Size	Survival
21	Gnanasekar et al. 2011 [49]	human prostate cancer cells (gene expression only)	Glycyrrhizin Ethyl Pyruvate (HMGB1 inhibitor)	↓	N/A	N/A	N/A
22	Wang et al. 2018 [50]	human lung cancer cells	Glycyrrhizin (HMGB1 inhibitor)	N/A	N/A	↓	N/A
23	Wu et al. 2018 [51]	human non-small cell lung carcinoma cells	Glycyrrhizin (HMGB1 inhibitor)	↓	N/A	↓	N/A
24	Qiu et al. 2019 [52]	mouse lung cancer cells	Glycyrrhizin (HMGB1 inhibitor)	N/A	↓	N/A	N/A
25	Yao et al. 2019 [53]	mouse lung injury	Glycyrrhizin (HMGB1 inhibitor)	N/A	↓	N/A	↑
26	Booth et al. 2017 [33]	human lung	Valproic acid (HDAC inhibitor)	N/A	↑	N/A	N/A
27	Li et al. 2018 [54]	mouse lung injury	Sodium butyrate (HDAC inhibitor)	N/A	↓	N/A	N/A
28	Luo et al. 2013 [55]	human colon cancer	Trichostatin A (HDAC inhibitor)	N/A	↓	↓	N/A

↑/↓: increase or decrease in levels of HMGB1; N/A: not assessed in study.

3. Results

3.1. HMGB1, the Proinflammatory Molecule

HMGB1 is a nuclear protein that has a structural role in DNA damage repair [56–59]. It is anchored in the nucleus by interactions between its nuclear localization sequence (NLS) and nuclear transport proteins. Although it normally participates in DNA repair, HMGB1 has also been demonstrated to inhibit DNA damage repair when exposed to platinum-based cancer therapeutics [56,60,61]. HMGB1's nuclear function and interactions with other nuclear proteins is a potential area for future research [62–64]; however, this review is largely focused on HMGB1's role outside of the cell.

While nuclear HMGB1 helps regulate gene expression and DNA repair, extracellular HMGB1 has a significant role as a proinflammatory molecule. HMGB1 belongs to a class of proteins called alarmins, also known as damage-associated molecular pattern (DAMP) molecules [65]. These proteins are active in a wide variety of pathologies that relate to cellular damage or distress. During infection or cellular damage, HMGB1 is transported out to the cytoplasm and into the extracellular space [17]. Several studies have described how exposure of immune cells to bacterial endotoxin leads to release of HMGB1 [66–68], while a more recent study demonstrated that HMGB1 secretion is mediated through processes tied to a type of programmed cell death known as pyroptosis that is characterized by activation of the NLRP3 inflammasome [69]. Therefore, HMGB1 release from cells is tied to multiple stimuli that illicit inflammatory processes.

HMGB1 localization is regulated through a series of post-translational modifications. Additions such as methylation, phosphorylation, and acetylation can alter how HMGB1 interacts with chaperone proteins and DNA, which in turn alters its localization and function [70,71]. For instance, phosphorylation of specific residues in HMGB1 alters its nuclear localization [72]. Similar observations have been made regarding acetylation. Acetylation is the most well-characterized modification of HMGB1. Acetylation of several lysine residues within both HMGB1 nuclear localization sequences (NLS1 and NLS2) regulates the secretion of HMGB1 to the extracellular space [72,73]. There are 17 lysine residues that can be modified by acetylation. It has been shown that residues 17, 28, and 29 in the NLS1, and 179, 181, 183, and 184 in NLS2 are the most frequently critical to acetylation-dependent nuclear export (Figure 2). Interestingly, secretion of HMGB1 does not require conventional secretory mechanisms involving the endoplasmic reticulum like other secreted cytolsolic molecules [74]. Instead, HMGB1 has been shown to be released via gasdermin-independent membrane pores generated during inflammasome activation [69]. Together, this supports the idea that NLS domains within HMGB1 may be potential candidates for targeted therapies for inflammatory disorders [68].

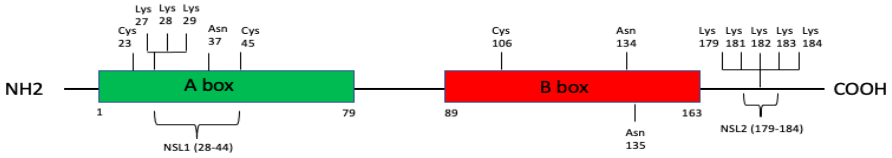

Figure 2. Sites of posttranslational modifications in the amino acid sequence of HMGB1.

Methylation has also been demonstrated to alter HMGB1 function. Unlike phosphorylation and acetylation, methylation affects the ability of HMGB1 to interact with DNA, while affecting its localization [70]. In addition to the aforementioned, there are two additional modifications of potential interest for future studies, namely glycosylation, and ADP-ribosylation. Glycosylation of HMGB1 appears to be limited to N-glycosylation of asparagine residues [74]. Glycosylation of HMGB1 influences interactions with an important binding partner chromosomal maintenance 1 (CRM1) in the nucleus. CRM1, also known as exportin 1, is a nuclear export protein. Glycosyl-moieties on HMGB1 promotes interactions between the two proteins and promotes movement of HMGB1 out of the nucleus [74]. In this way, it is possible that glycosylation may be equally as important

as acetylation to HMGB1 movement. The last protein modification to discuss here is ADP-ribosylation (PARylation). PARylation is a more recently identified modification of HMGB1, but it has also been demonstrated to be important to the process of nuclear export and the release of HMGB1 during necrotic cell death [66,70]. PARylated HMGB1 amplifies the pro-inflammatory capacity of HMGB1. It does this in part by facilitating the interaction of HMGB1 with RAGE receptors, which signal to activate the transcriptional activity of NF-kB [39,75].

The extracellular function of HMGB1 is dictated by its redox state. Key cysteine residues in the HMGB1 protein are responsible for its redox sensitivity. Three residues (cysteine 23, 45, and 106) are all fully reduced in the nucleus [76]. Movement of HMGB1 out of the nucleus leads to the subsequent oxidation of these cysteines, two of these residues (23 and 45) form disulfide bonds [76,77]. Fully oxidized HMGB1 has less pro-inflammatory capacity than its reduced form. This is likely because reduced HMGB1 is not actively released from cells, unless they are damaged or dying, as opposed to the active secretion of the oxidized form [76]. Partially oxidized HMGB1 has more inflammatory potential and interacts with a few different extracellular receptors, taking part in various cellular processes. Based on these interactions, extracellular HMGB1 serves as a ligand for cell surface receptors and promotes the expression of cytokines. These cytokines are hallmarks of inflammation and are present at elevated levels in human diseases like obesity and cancer, further illustrating the central role HMGB1 has as a critical mediator of systemic inflammation.

3.2. HMGB1 as a Therapeutic Target

Inflammation is a major component of the innate immune response designed to prime the body to fight potential infection or eliminate damaged or aged tissues. HMGB1 is a part of that response and is actively secreted by activated macrophages and other cells [17,68]. HMGB1 can be released by activated inflammatory cells and may even accumulate during infection or injury. Once released, extracellular HMGB1 is a ligand for multiple cell surface receptors (RAGE, TLR2, and TLR4) [25,78–80]. Interactions with RAGE, TLR2, or TLR4 by HMGB1 leads to the phosphorylation and activation of kinases interleukin-1 receptor associated kinases (IRAKs, IRAK1, 2, and 4) and mitogen-activated protein kinases (MAPKs, such as p38, JNK, and ERK) that activate the downstream transcription factors AP-1 and NF-κB, leading to proliferative and inflammatory responses [53,81]. This signaling cascade leads to additional release of HMGB1 and ultimately the increased expression of NF-kB target genes such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1β (IL-1β), and interferon gamma (IFN-γ) [42]. TNF-α, IL-6, and IL-8, promote tumor growth through TLR-mediated signaling pathways, thus promoting ERK1/2, NF-κB, and STAT3 activation [40].

The role of inflammation in initiating malignant disease is well established. As such, we thought it was critical to include an example of non-malignant inflammatory lung dysfunction to highlight the roles of HMGB1 in disease. Acute lung injury (ALI) is a type of respiratory failure marked by the rapid and widespread onset of inflammation throughout the lungs. Disease progression in ALI is characterized by cytokine mediated inflammation through increasing HMGB1 production as well as proinflammatory cytokines like TNF-α, IL-6, and IL-8 through NF-κB activation [43,44]. In a mouse model of lung injury, circulating HMGB1 and the elevated NF-κB activity was associated with disease severity, suggesting that HMGB1 could be used to monitor disease progression [42]. The systemic inflammatory response observed in ALI is similar to what is seen in the tumor microenvironment. Across many disease models, the importance of understanding the role of extracellular HMGB1 in disease outcomes has become increasingly evident. Due to the positive feedback that inflammation has on HMGB1 secretion, HMGB1 tends to amplify inflammatory responses in various pathological conditions [44]. While studies have shown that inflammatory cytokines mediate acute lung injury (ALI), increased serum levels of HMGB1 are associated with worse prognosis [43]. Often increased levels of HMGB1 are

correlated with the RAGE receptor and its role in promoting the phenotype associated with many inflammatory diseases and various tumors.

As mentioned earlier, HMGB1 signaling via RAGE and TLRs leads to activation of NF-κB; however, NF-κB is not only a mediator of inflammation, but also has an important factor in tumor survival. NF-κB activity can antagonize programmed cell death and promote mitogenic signaling, which both are advantageous to growing cancer cells [40]. This was evident in studies that highlighted the relationship between HMGB1 and cancer metastasis in xenograft models for lung cancer [50]. HMGB1 released from apoptotic cancer cells, following administration of chemotherapeutic drugs, was complexed with nucleosome DNA. These HMGB1-DNA complexes were suitable ligands for another member of the toll-like receptor family, TLR9 [19,35]. HMGB1 binding TLR9 led to increased metastasis in animal models of human lung cancer. This would suggest that treating patients with chemotherapeutic drugs could lead to subsequent metastatic cancer events. This idea is supported by evidence that patients undergoing chemotherapy treatments have significantly elevated levels of HMGB1-nucleosomes in their blood. Taken together, these results strongly support the exploration of methods to inhibit extracellular HMGB1 activity in patients to improve outcomes.

3.3. Blocking the Release of HMGB1 Using Anti-Inflammatory Therapeutics

Therapeutics that have anti-inflammatory properties have been shown to inhibit the release of HMGB1. Among those are ethyl pyruvate and glycyrrhizin. Release of HMGB1 is blocked when ethyl pyruvate suppresses HMGB1/RAGE axis in liver, pancreatic and non-small cell lung cancer leading to decreased cell growth [37–41]. In addition to ethyl pyruvate suppressing HMGB1 protein release, it decreases RAGE receptor expression, which leads to a decrease in HMGB1-mediated cell proliferation [42]. HMGB1 release is also reduced with ethyl pyruvate treatment of cervical cancer cells, resulting in increased intracellular HMGB1 and decreased cell proliferation causing increased levels of HMGB1 inside the cell [34].

Similarly, glycyrrhizin, a naturally occurring inhibitor of HMGB1 found in licorice, acts as an anti-inflammatory therapeutic and blocks the release of HMGB1. Glycyrrhizin has been shown to inhibit growth in lung cancer cells [48,51]. It directly interacts with the two shallow concave surfaces formed by the arms of the HMGB1 box regions [47]. Glycyrrhizin inhibits HMGB1 accumulation in the extracellular space, and prevents its interaction with proinflammatory receptors like TLR4, TLR2, and RAGE receptors [82–85]. Diseases where inflammation is a major factor in pathogenesis such as oncogenic transformation, bacterial infection, or diet-induced symbiosis are also sensitive to treatment with glycyrrhizin [46,49,52,53]. Conversely, the anti-inflammatory transforming growth factor (TGF-B1) pathway has been implicated in the cellular retention of HMGB1. Epithelial-mesenchymal transition (EMT) promotes cell migration, invasion, and ultimately metastasis. TGF-B1 drives EMT through increased vimentin expression, decreased E-cadherin expression, which is associated with subsequent HMGB1 release [47]. Treatment of cells undergoing EMT with glycyrrhizin increased HMGB1 retention and restored E-cadherin levels. In nasal epithelial cells, glycyrrhizin cooperated with sirtuin 6 (SIRT6), a protein deacetylase, and inhibited translocation of HMGB1 from the nucleus, preventing extracellular release [48].

Therefore, several lines of evidence illustrate that cellular retention of HMGB1 increases in the cells exposed to glycyrrhizin or ethyl pyruvate.

3.4. HDAC Inhibitors Increasing HMGB1 Release

As previously mentioned, deacetylases (i.e., SIRT6) cooperate to regulate aspects of HMGB1 biology, making modulating their function an attractive method to control HMGB1. Histone deacetylases (HDAC) inhibitors are a class of compounds that increase the acetylation of lysine residues on histone proteins by inhibiting the activity of HDAC enzymes. In cancer, HDAC inhibitors inhibit the proliferation of tumor cells in culture and in-vivo by

inducing apoptosis and cell cycle arrest [85]. Cellular localization of HMGB1 is dictated by the presence or absence of acetyl groups on the protein. HMGB1 release occurs in cells that are undergoing necrosis or inflammasome activation [86]. Regulation of deacetylase enzymes is a rational approach to preventing active release of HMGB1 [33]. HMGB1 release occurs in cells that are undergoing necrosis or inflammasome activation [87]. Regulation of deacetylase enzymes is a rational approach to preventing active release of HMGB1.

HDAC inhibitors, including AR-42, trichostatin A, sodium butyrate, and sodium valproate (valproic acid), promote release of HMGB1 [54,55,88]. Melanoma cells containing B-raf mutations have been shown to have sensitivity to HDAC inhibition. The sensitivity may be linked to the decreased levels of HMGB1 following HDAC inhibition. In many tumors, pemetrexed and sildenafil promoted the extracellular release of HMGB1 [88]. In fact, pemetrexed and sildenafil-mediated lethality was enhanced by the addition of HDAC inhibitors AR-42 and valproic acid in lung cancer models. In metastatic human breast cancer cells, increased HMGB1 cytoplasmic accumulation and release also occurred following treatment with HDAC inhibitors [32]. Together, these data demonstrate that the relationship between HMGB1 and acetylation is key to important aspects of tumor development. Therefore, this is additional evidence indicating the need to investigate ways to regulate HMGB1 in vivo to improve response to therapy and increase overall survival.

4. Discussion

HMGB1 is a multifaceted protein with roles in genomic stability and immune response. As research on HMGB1 has expanded, it has become clear that HMGB1 is involved with several key pathways necessary for normal cell function. Yet in tumorigenesis, the role of HMGB1 appears to be important, but still incompletely understood. Currently, the research is divided on whether HMGB1 is a benefit or detriment to the development of malignant neoplasia. This is due, in part to the role of HMGB1 in DNA damage repair in the nucleus, inflammatory signaling in the extracellular space, and immunosuppression in coordination with regulatory T cells [36]. As immunotherapy for cancer becomes more widely available, it is becoming even more critical to understand the mechanisms that tumors employ to evade immunosurveillance and prevent natural defenses from eliminating growing malignancies. For instance, HMGB1 promotes an immunosuppressive environment by stimulating the expression of immune checkpoint molecule PD-L1 in melanoma cells [89]. Conversely, and most relevant to the intent of this review, combinations of small molecules inhibitors of HMGB1 along with anti-PD-L1 therapy improved the overall efficacy of the cancer immunotherapy [90]. These data suggest that HMGB1 is potentially a synergistic molecular target for immunotherapy in solid tumors. However, there are currently gaps in the literature that need to be filled to demonstrate the proof of concept for therapeutic use of anti-HMGB1 drugs as therapeutically valuable. Robust pre-clinical studies are needed to validate this strategy in human patients. In support of such an approach, extracellular HMGB1 is readily detectable by immunological assays, which could allow clinicians to determine the utility of inhibitors using minimally invasive procedures.

The studies cited in this review utilize several compounds that have an inhibitory effect on HMGB1. Based on our survey of the available literature involving HMGB1-targeting in lung cancer using in vivo and in vitro models, there was limited research identified in this area, which signifies the gap in knowledge and an opportunity to observe the role of HMGB1 inhibition and its role in cancer in clinical and pre-clinical models. The inhibitors included in this review (glycyrrhizin, valproic acid, ethyl pyruvate) are all compounds that are known to be reasonably safe in humans and have at least some evidence of providing benefit to patients with a variety of different maladies. Our hope is that based on this summary of the available research, it has become clearer that incorporating HMGB1 into strategies for treating solid tumors is an underutilized approach that could have significant benefit for disease outcomes.

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