Comprehensive analysis of the mechanism and treatment significance of Mucins in lung cancer

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Abstract
Aberrant expression of mucin proteins has played a complex and essential role in cancer development and metastasis. Members of the mucin family have been intimately implicated in lung cancer progression, metastasis, survival and chemo-resistance. During the progression of lung cancer, mucin proteins have involved all of the procession of lung cancer, which is interacted with many receptor tyrosine kinases signal pathways and mediated cell signals for tumor cell growth and survival. Mucins thus have been considerable as the indicator of negative prognosis and desirable therapeutic targets of lung cancers. In this review, we comprehensively analyzed the role of each member of the mucin family in lung cancer by combining open-accessed database analysis and assembling cutting-edge information about these molecules.

Keywords: Lung cancer, Mucins, Biomarkers, Treatment of lung cancer

Background
Lung cancer has ranked the most common cause of cancer death worldwide. Every year, there are about 1.8 million people being diagnosed with lung cancer, and 1.6 million people died from the disease [1]. Approximately 85% of patients had a group of histological subtypes collectively known as non-small cell lung cancer (NSCLC), in which lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) have been the most common subtypes [2]. Recently significant advancement has been made in the driver genes research, screening biomarkers, and personalized therapy (precision medicine) of lung cancer, the 5-year relative survival rate for lung cancer has been 19% overall (16% for men and 23% for women); 24% for non-small cell; and 6% for small cell tumors [3]. However, there still remain several challenges as following: we need to identify new driver gene alterations to expand the population benefited from targeted therapies; It is important to understand the mechanisms responsible for resistance to targeted therapy for further prevention or overcoming; also better predictors of responses to immunotherapy, new drugs and rationally designed drug combination therapies need to screen [4].

Mucins are classified into two major categories depended on their structure-membrane mucins and secreted mucins. The membrane mucins are consisted of eleven members as MUC1, MUC3A, MUC3B, MUC4, MUC12, MUC13, MUC15, MUC16, MUC17, MUC20 and MUC21; while secreted mucins are comprised of seven members which can be further subdivided into gel-forming mucins (MUC2, MUC5AC, MUC5B, MUC6, MUC19) and non-gel-forming mucins (MUC7, MUC8). All mucin members have at least one mucin-like domain which contains a high proportion of tandem repetitive structures of prolines, threonines and serins (which form the PTS domain). And the PTS domain of the mucins is extensively glycosylated at the threonine
and serine residues through GalNAc O-linkages. The two kinds of mucins have different functions in the human body. The membrane mucins are located in the ductal surfaces of organs epithelial cells served as a physical barrier. The transmembrane mucins are primarily located on the apical membrane of epithelial cells, where they could play a role in cell signaling. They all protect the integrity of epithelial cells from different environmental stresses. For example, they could degraded enzymes by forming a physical, chemical and immunological barrier and interact with many receptor tyrosine kinases mediated cell signals [5]. Any alteration of MUCs expression or glycosylation pattern will significantly affect tumor cell growth, differentiation and survival which enabled them regard as potent cancer-inducing molecules [5–7].

In this review, we have drawn an overview of the mucin family and discussed the role of each mucin members in tumorigenesis and metastasis and recent advances in tumor research. We will concentrate on the importance of mucin proteins on cellular signaling pathways and its role in targets and immune therapy of lung cancer.

Expression and mutation landscape of Mucins in NSCLC
TCGA-GTEx mixed data Cohort, which contained 1410 lung cancer and normal lung tissue samples was downloaded from UCSC Xena [8–10] to analyze Mucins expression (Fig. 1a). According to our analysis, we found that MUC1, MUC2, MUC3AC, MUC4, MUC5AC, MUC5B, MUC6, MUC13, MUC15, MUC16, MUC20, MUC21, MUC22 elevated than normal lung tissue while MUC7 decreased in LUAD. However, in LUSC, MUC1, MUC3AC, MUC5AC, MUC6, MUC7, MUC15, MUC17, MUC21 indicated lower expression compared with normal lung tissue, while MUC4, MUC13, MUC16, MUC20

![Fig. 1 Mucins expression and mutation in non-small cell lung cancer.](image-url)

*P < 0.05, **P < 0.01, ***P < 0.0001*
increased. These results somewhat have contradicted with the existing research that each of MUC1 and MUC5AC had a high protein expression in lung carcinoma. Lappi-Blanco et al. summarized the MUC1 expression in lung cancer, which found high expression of MUC1 predicts poor survival in the majority of studies [11]. Especially, Guddo et al. and Woenckhaus et al. demonstrated MUC1 expression was associated with poor prognosis in squamous cell cancers patients [12, 13]. Considering to MUC5AC, Yu et al. identified MUC5AC overexpressed in stage I/II NSCLC patients [14, 15]. In addition, both MUC1 and MUC5AC have higher expression in adenocarcinomas compared with squamous cell carcinomas [14, 16]. However, our analysis based on public databases indicated that both MUC1 and MUC5AC mRNA overexpressed in LUAD, but decreased in LUSC. Hence, it is necessary to study the function of Mucins in LUAD and LUSC separately.

The mutation analysis based on the cBioportal [17, 18] had performed in Lung Adenocarcinoma (Broad, Cell 2012), Lung Adenocarcinoma (MSKCC, Science 2015), Lung Adenocarcinoma (TCGA, PanCancer Atlas) and Lung Squamous Cell Carcinoma (TCGA, PanCancer Atlas). 784 LUAD samples and 469 LUSC samples were incorporated. The results demonstrated that MUC4 (34% Amplification), MUC16 (41%), MUC17 (20% Missense), MUC20 (31% Amplification), MUC5B (14% Missense) existed high mutation rates in LUSC patients while in LUAD patients there had been high mutation in MUC5B (11% Missense), MUC16 (42% Missense), MUC17 (20% Missense). In addition, MUC16 and MUC17 have been the top 10 mutated genes of LUAD, and MUC16, MUC17 and MUC5B have been the top 50 mutated genes in LUSC (Fig. 1b). It has recently reported that co-occurring genomic alterations as mediators of diverse NSCLC phenotypes impacted molecular stratification framework shave, which emerged as a major tenets of the molecular diversity of NSCLC [19]. Therefore, we assessed the relationship between MUC mutation (Table 1). In LUAD, MUC5B were co-occurrence with MUC2, MUC6, MUC16, and MUC17; MUC16 existed co-occurrence with MUC2, MUC3A; MUC17 had co-occurrence with MUC2 and MUC12. In LUSC, MUC4 had co-occurrence with MUC20, MUC12 had co-occurrence with MUC17; and MUC21 had co-occurrence with MUC22.

Effects of Mucins on cellular signaling pathways

The overexpression of MUC1 causes many downstream indications closely related to poor clinical performance (Fig. 2). Giatromanolaki et al. examined the correlation between VEGF and MUC1 expression in 199 NSCLCs, then demonstrated that MUC1 expression is linked to high VEGF expression [20]. And overexpression of MUC1 facilitates angiogenesis of NSCLC by activating the Akt and ERK signaling pathways then up-regulating vascular endothelial growth factor (VEGF) [21]. Gao et al. demonstrated that knockdown MUC1 could activate apoptosis and inhibit cell proliferation and metastasis, as well as be sensitized to cisplatin treatment by modulating STAT3/Akt, SRC/FAK and Bcl-XL/Bcl-2 signaling pathways in NSCLC [22]. Besides, MUC1 could interact with ERα and ERβ within the nucleus of to inhibit the proliferation of LUAD cells [23]. MUC1 is also

| Cancer | A | B | Neither | A Not B | B Not A | Both | Log2 Odds Ratio | p-Value | q-Value | Tendency  |
|--------|---|---|---------|---------|---------|------|----------------|---------|---------|-----------|
| LUAD   |   |   |         |         |         |      |                |         |         |           |
| MUC2   | MUC16 | 404 | 21 | 265 | 38 | 1.464 | < 0.001 | 0.003 | Co-occurrence |
| MUC3A  | MUC16 | 421 | 4  | 284 | 19 | 2.816 | < 0.001 | < 0.001 | Co-occurrence |
| MUC5B  | MUC16 | 395 | 30 | 244 | 59 | 1.671 | < 0.001 | < 0.001 | Co-occurrence |
| MUC12  | MUC17 | 580 | 0  | 137 | 11 | > 3   | < 0.001 | < 0.001 | Co-occurrence |
| MUC16  | MUC17 | 368 | 212| 57  | 91 | 1.471 | < 0.001 | < 0.001 | Co-occurrence |
| MUC2   | MUC17 | 542 | 38 | 127 | 21 | 1.238 | 0.003 | 0.032 | Co-occurrence |
| MUC5B  | MUC17 | 521 | 59 | 118 | 30 | 1.167 | 0.001 | 0.013 | Co-occurrence |
| MUC3A  | MUC20 | 687 | 19 | 18  | 4  | > 3   | 0.004 | 0.035 | Co-occurrence |
| MUC4   | MUC20 | 663 | 43 | 1   | 21 | > 3   | < 0.001 | < 0.001 | Co-occurrence |
| MUC21  | MUC22 | 712 | 10 | 0   | 6  | > 3   | < 0.001 | < 0.001 | Co-occurrence |
| MUC2   | MUC5B | 599 | 40 | 70  | 19 | 2.023 | < 0.001 | < 0.001 | Co-occurrence |
| MUC5B  | MUC6  | 620 | 79 | 19  | 10 | 2.046 | 0.001 | 0.014 | Co-occurrence |
| MUC3A  | MUC7  | 681 | 14 | 24  | 9  | > 3   | < 0.001 | < 0.001 | Co-occurrence |
| LUSC   |   |   |         |         |         |      |                |         |         |           |
| MUC4   | MUC20 | 306 | 18 | 5   | 140| > 3   | < 0.001 | < 0.001 | Co-occurrence |
| MUC12  | MUC17 | 373 | 0  | 76  | 20 | > 3   | < 0.001 | < 0.001 | Co-occurrence |
| MUC21  | MUC22 | 456 | 9  | 0   | 4  | > 3   | < 0.001 | < 0.001 | Co-occurrence |
involved in the NF-κB signaling pathways by forming a complex with NF-κB/p65. The complex is directly brought to the promoter of CD274 driving PD-L1 transcription [24]. Another complex, MUC1/β-catenin/TCF4 is directly bound to the MYC promoter and promotes the recruitment of p300 histone acetylase (EP300), which can induce histone H3 acetylation and MYC gene transcription, in turns downregulate MYC-target genes [25]. MUC1-C induces NF-κB/p65 chromatin occupancy of the LIN28B first intron and activates LIN28B transcription, consequently activates the LIN28B → let-7 → HMGA2 ceRNA axis in NSCLC, and thereby promotes EMT and stemness phenotype [26]. The N-glycosylated MUC1-C restrains miR-322 expression and thereby upregulates galectin-3. Successively, galectin-3 forms a bridge between MUC1 and the EGFR which physically integrates MUC1 with EGFR signaling [27]. Moreover, MUC1 plays a great role in acquired chemoresistance. In the study of Xu et al. demonstrated that knockout MUC1 could significantly increase the apoptotic toxicity of displaying, doxorubicin and TRAIL induced anti-apoptotic lung cancer cells. And miR-551b/catalase/ROS axis gives rise to MUC1 overexposure following EGFR-mediated activation of the cell survival cascade involving Akt/c-FLIP/COX-2 [28]. In PTX-resistant lung cancer cells, overexposure of MUC1 promotes proliferation, stemness by regulating PI3K/Akt signaling and cancer stemness biomarkers [29]. Similarly, MUC4 drops lung cancer cells proliferation through down-regulating of cell cycle related protein and GSK3β/p-Akt, which regulates the invasion and metastasis by FAK activity and EMT marker [30]. MUC5AC interacts with integrin β4 recruit phosphorylation of FAK (Y397) activated downstream signaling pathways, leading to lung cancer cell migration [31]. Wei Han et al. demonstrated knockdown MUC5AC could significantly downregulate PCNA which is a well-known proliferation biomarker, and metastasis biomarker MMP-2, MMP-9 [15]. MUC16 could promote lung cancer progression, metastasis, and chemoresistance to cisplatin and gemcitabine via the regulation
Regulation of the expression of Mucin family genes

There are still various transcription factors and signaling molecules regulating MUC1 gene expression in airway epithelial cells and lung cancer cells (Fig. 3). Sp-1 has been demonstrated to modulate MUC1 expression by being peculiarly binding on the MUC1 promoter between −99/−90 in lung cancer cells [35]. Hypoxia activates the HIF-1α interacted with MUC1 promoter then enhances MUC1 expression [36]. The downregulation of 14–3-3ζ could completely clear up the carcinogenic potential of MUC1 through MUC1/NF-κB feedback loop [37]. Fuzhengkangai decoction regulates MUC1 expression through Akt-mediated inhibition of p65 [38]. Besides, STAT3 and DPP9 are two upstream regulators of MUC1 which can regulate MUC1 expression at both mRNA and protein levels [22, 39]. EGF and TGF-α induces MUC2 and MUC5AC expression through EGFR/Ras/Raf/ERK-signaling Cascade. In addition, Sp-1 and Sp-3 regulates MUC2 and MUC5AC expression by binding their promoters [40]. PRDM16-ΔPRD regulates transcription of MUC4 by regulating the histone modifications of its promoter [41]. SPDEF regulates the expression of MUC5AC and MUC5B combining with the upstream enhancer regions of the MUC5AC and MUC5B [42]. Besides, two long non-coding RNA have been reported involved in regulating mucins. SNHG16-miR-146a axis stimulate MUC5AC expression in NSCLC [15]. MUC5B-AS1, as a novel long non-coding antisense transcript, promotes cell migration and invasion by forming a RNA-RNA duplex with MUC5B, thereby increases MUC5B expression levels in lung adenocarcinoma [43].

The importance of Mucin for the tumor immune microenvironment

Recently, cancer immune microenvironment has proved of great significance for immunotherapy. Several studies have reported that evaluating MUC1 in tumor cells is relating to the evasion of immune recognition and destruction in NSCLC (Fig. 2). MUC1 plays a key role in TAM-induced in the generation of lung cancer stem cells (LCSCs) progression by regulating NF-κB, CD133, and Sox2 [44]. Targeting MUC1-C drives the aberrant downregulation of PD-L1, IFN-γ and leads to enhanced effector function of CD8+ tumor-infiltrating lymphocytes (TILs) in the tumor microenvironment [45]. Knockdown MUC1-C inhibits PD-L1 and TLR9, IFN-γ, MCP-1 and GM-CSF expression in NSCLC tumors [24]. Furthermore, the connection between the immune infiltration levels and the expression of mucins in LUAD and LUSC patients was discussed based on TIMER (Fig. 4a-b) [46, 47]. MUC1 mRNA expression was

Fig. 3 Schematic diagram of signaling pathways other mucins involved in non-small cell lung cancer. MUC5AC implicated in activating FAK and AKT pathways. MUC4 promote the proliferation and metastasis of lung cancer through regulation cell cycle related genes and EMT. MUC16 regulated the transcription of TSPYL5 via JAK/STAT3 and PS3 pathways. Moreover, EGFR regulated the MUC2/5 AC expression through ERK pathway.
significantly positively correlated with infiltrating levels of macrophages, Netrophil and Dentritic cells, and MUC6 mRNA expression level showed a significantly positively correlation with CD4+ T cells in LUSC. In LUAD, MUC16 mRNA expression indicated the association with CD4+ T-cells, Netrophil. MUC4 has a negative correlation with Dentritic Cells and CD8+ T cells. And MUC21 positively correlates with Dentritic Cells.

Mucins and therapeutic perspectives

Various studies demonstrated that MUC1 plays an important role in drug-resistance, targeted therapy of lung cancer, which makes it an attractive target for lung cancer therapy. The MUC1 inhibitor GO-201, 202 and 203 can bind directly with the cytoplasmic domain of MUC1 thereby weaken MUC1-mediated cell proliferation [48]. And, GO-203 blocks homoerotic dimerization of MUC1-C, and reverses the MUC1 carcinogenic effect in NSCLC [49]. Several studies have reported how GO-203 work in NSCLC. GO-203 inhibits NSCLC cell growth and survival by preventing the integration between MUC1-C and PI3K-p85, and suppresses constitutive phosphorylation of Akt and its downstream effector, mTOR [48]. Furthermore, GO-203 also plays an important role in the regulation of EGFR-TKI resistance treatment. Silencing MUC1-C in H1975/EGFR(L858R/T790M) cells suppresses AKT signaling pathway, and inhibits cell proliferation of lung cancer [50]. Combining GO-203 with afatinib work synergistically can inhibit the growth of NSCLC cells with EGFR(T790M) or EGFR (delE746-A750) mutants [50]. Combining GO-203 with JQ1 which mechanically inhibits MYC expression shows synergistic function in inhibiting growth of NSCLC tumor xenografts [25]. Silencing MUC1-C in KRAS(G12S) and KRAS(Q61H) mutated NSCLC cells results in downregulation of AKT and MEK signaling and represses ZEB1/miR-200c loop, thereby reverses the EMT phenotype, decreases self-renewal and attenuates the proliferation of KRAS mutant NSCLC cells [51]. Most of all, treatment with GO-203 destroy the MUC1-C→PD-L1 signaling, and promotes the suppression of CD8+ T cell activation [45]. Integrating GO-203 with immune checkpoint inhibitors may be a potential approach for NSCLC therapy.

MUC1 also serves as TAAs playing an important role in tumor immunotherapy. There are two vaccines for NSCLC targeted MUC1 being in clinical trials. TG4010 is an immunotherapeutic vaccine based on Modified Vaccinia virus Ankara (MVA), and encoding the human tumor-associated antigen MUC1 and human IL-2. In Phase II study of TG4010, there were 65 patients with MUC1 positively treated with TG4010 in combination with cisplatin and vinorelbine as first-line chemotherapy. The median overall survival (OS) was 12.7 months and 14.9 months respectively [52]. In the study of Quoix et al. (NCT00415818), 148 patients with advanced (stage IIIB or IV) NSCLC with MUC1 positively were enrolled in parallel groups, that patients in experiment treated were allocated to the combination therapy group, and received TG4010 plaque forming with TG4010 plus cisplatin and gemcitabine while the control group received the same chemotherapy alone. The 6-month progression-free survival (PFS) was 43.2% in the TG4010 plus chemotherapy group, and 35.1% in the chemotherapy alone group [53]. In another study of Quoix et al. (NCT01383148), they
recruited 222 patients and randomly allocated averagely into TG4010 and chemotherapy, placebo and chemotherapy 111 groups. The results indicated that median PFS was 5.9 months in the TG4010 group and 5.1 months in the placebo group [54]. Both of these studies demonstrated TG4010 plus chemotherapy improve PFS and OS outcome in MUC1-positive patients. Recently, a study of 78 patients which all coming from the TIME study carrying the HLA-A02*01 haplotype indicated TG4010 treatment broadens CD8+ T cell against responses to MUC1 as well as other non-targeted TAA [55]. Therefore, TG4010 can be used in combination with other targeted immunomodulators to maximize response rates and clinical benefits. Sequential treatment with anti-PD-1/PD-L1 after treated with TG4010(NCT02823990) shows a better overall survival in mice model [56]. Moreover, there are two clinical trials (NCT02823990 and NCT03353675) in studying about combing TG4010 and Nivolumab in NSCLC patients (Table 2).

Table 2: Current recruiting and non-recruiting clinical trials of mucins

| Drug Name | Clinical trial ID | Phase | Clinical trial |
|-----------|------------------|-------|----------------|
| TG4010+ chemotherapy | NCT00415818 | Phase 2/3 | A Phase IIb Multicentric Controlled Study Evaluating the Therapeutic Vaccine TG4010(MVA-MUC1-IL2) as an Adjunct to Standard Chemotherapy in Advanced Non-Small Cell Lung Cancer |
| TG4010 + placebo | NCT01383148 | Phase 2/3 | A Phase II/III Randomized, Double-blind, Placebo Controlled Study Comparing First Line Therapy with or Without TG4010 Immunotherapy Product in Patients with Stage IV NSCLC |
| TG4010 + Nivolumab | NCT02823990 | Phase 2 | Phase II Trial of TG4010 Plus Nivolumab in Previously Treated Patients with Metastatic NSCLC |
| TG4010 + Nivolumab | NCT03353675 | Phase 2 | A Phase II Study Evaluating the Efficacy and the Safety of First-line Chemotherapy Combined with TG4010 and Nivolumab in Patients with Advanced Non-squamous NSCLC |
| Tecemotide (L-BLP25) | NCT00157196 | Phase 2 | A Multi-center, Non-randomized, Open Label Safety Study of BLP25 Liposome Vaccine (L-BLP25) in NSCLC Patients with Unresectable Stage III Disease |
| Tecemotide (L-BLP25) | NCT00157209 | Phase 2 | A Multicenter Phase IIb Randomised, Controlled Study of BLP25 Liposome Vaccine for Active Specific Immunotherapy of NSCLC |
| Tecemotide | NCT00409188 | Phase 3 | A Multi-center Phase III Randomized, Double-blind Placebo-controlled Study of the Cancer Vaccine Stimuvax® (L-BLP25 or BLP25 Liposome Vaccine) in NSCLC Subjects with Unresectable Stage III Disease. |
| Tecemotide (L-BLP25) | NCT01015443 | Phase 3 | A Multi-national, Double-blind, Placebo-controlled, Randomized, Phase III Clinical Trial of the Cancer Vaccine Stimuvax® (L-BLP25 or BLP25 Liposome Vaccine) in Asian Subjects with Stage III, Unresectable, NSCLC Who Have Demonstrated Either Stable Disease or Objective Response Following Primary Chemo-radiotherapy |
| Tecemotide | NCT02049151 | Phase 3 | A Multicenter, Randomized, Double-blind, Placebo-controlled Phase III Trial of Tecemotide Versus Placebo in Subjects with Completed Concurrent Chemo-radiotherapy for Unresectable Stage III NSCLC |
| Tecemotide | NCT00960115 | Phase 1/2 | Combined Phase I/II Clinical Study of EMD531444(L-BLP25 or BLP25 Liposome Vaccine) in Subjects with Stage III Unresectable Non-Small Cell Lung Cancer Following Primary Chemoradiotherapy |
| Tecemotide+Bevacizumab | NCT00828009 | Phase 2 | A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer After Definitive Chemoradiation |
| Tecemotide | NCT01423760 | Not Applicable | An Open-label Trial to Collect Long-term Data on Subjects Following Participation in Previous EMD 531444 (L-BLP25 or BLP25 Liposome Vaccine) Clinical Trials |
| ETBX-051 + ETBX-061 + ETBX-011 | NCT02140996 | Phase 1 | Multi-Targeted Recombinant Ad5 (CEA/MUC1/Brachyury) Based Immunotherapy Vaccine Regimen in People with Advanced Cancer |
| anti-MUC1 CAR T cells | NCT03525782 | Phase 1/2 | A Clinical Study of Anti-MUC1 CAR T Cells and PD-1 Knockout Engineered T Cells for Patients with Advanced Non-small Cell Lung Cancer |
| anti-MUC1 CAR-pNK cells | NCT02839954 | Phase 1/2 | Study Evaluating the Efficacy and Safety of Chimeric Antigen Receptor-Modified pNK Cells in MUC1 Positive Advanced Refractory or Relapsed Solid Tumor |
| anti-MUC1 CAR T cells | NCT02587689 | Phase 1/2 | Phase II Study of Anti-MUC1 CAR T Cells for Patients with MUC1+ Advanced Refractory Solid Tumor |
| CART-TnMUC1–01 | NCT04025216 | Phase 1 | A Study of CART-TnMUC1 in Patients with TnMUC1-Positive Advanced Cancers |
| MUC1 Peptide-Poly-ICLC | NCT03300817 | Phase 1 | A Pilot Study of MUC1 Vaccine in Current and Former Smokers at High Risk for Lung Cancer |
| MUC1 peptide-poly-ICLC | NCT01720836 | Phase 1/2 | Vaccine Therapy in Treating Patients with Stage III Non-Small Cell Lung Cancer |
Tecemotide, also known as L-BLP25 or Stimuvax, is designed to elicit an antigen-specific cellular immune response against MUC1, which is one of the first TAAs identified by human tumor-specific T-cells. Palmer M et al. performed a phase 1 study of L-BLP25 in patients with stage IIB or IV NSCLC, which certified that L-BLP25 were well tolerated for patients [57]. Later, Charles Butts et al. conducted a Phase II Trial in stage IIB or IV NSCLC patients, which patients were treated with either L-BLP25 plus best supportive care (BSC) or BSC alone. The 3-year following up results demonstrated a median survival time was longer in patients treated with L-BLP25 plus BSC compared with BSC alone, and patients in stage IIB LR disease showed the greatest difference [58, 59]. The phase 3 Trial of L-BLP25, which recruited 1513 patients with Stage III NSCLC (NCT00409188), the results demonstrated that patients treated with L-BLP25 have longer median OS (25.6 months) versus placebo (22.3 months), combined L-BLP25 with chemoradiotherapy had a markedly longer median OS (30.8 months) than placebo (20.6 months) while sequential chemoradiotherapy with L-BLP25 (19.4 months) shows no difference versus placebo (24.6 months) [60]. Conversely, Phase I/II Study of Nobuyuki et al. in Japanese unresectable Stage III NSCLC (NCT00960115) found that L-BLP25 has no greater treatment effect in individuals than those received primary concurrent chemoradiotherapy [61]. However, there are still various clinical trials of L-BLP25 under study about CAR T cells therapy and Vaccine for prevention for lung cancer (Table 2).

Conclusions

Although mucins in lung cancer are not well studied because of its heavy molecular weight, they are still tended to play a significant role in lung carcinogenesis. Mucins served as an important diagnostic method is widely used in clinical especially MUC1 and MUC16 due to their unique expression pattern and function. And their therapeutic potential in lung cancer deserve further studies. And the association between different Mucins will make a specific degree of sophistication in our understanding to their function in lung carcinogenesis.

MUC1-targeted vaccines and small molecule drugs are now in clinical studies for preventing lung cancer. However, the effect of those vaccines was rarely as expected, which makes it necessary to develop new drugs for MUC1 or other mucins. Moreover, it seems that MUC16, MUC21 and MUC5B showed high mutation rates, mRNA expression and close relations to tumor immune infiltration may be still a great target for lung cancer target and immune therapy.

In addition, further researches about the role of mucins in lung cancer with different mutational background such as K-ras, EGFR, and BRAF are necessary to guide the combination therapy and overcome drug-resistance for lung cancer.
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