World Journal of Biomedical Sciences
ISSN:2960-0189
DOI:10.61784/wjbs231240

TOBACCO SMOKE EXPOSURE COMBINED WITH GENETICALLY ENGINEERED MICE COPD DRUGS APPLICATION PROGRESS OF TARGET AND MECHANISM RESEARCH

S. Lungwitz
Department of Pharmaceutical Technology, University of Regensburg, Regensburg, Germany.

Abstract: Chronic obstructive pulmonary disease (chronic obstructive pulmonary disease) pulmonary disease, chronic obstructive, COPD) is a common respiratory disease that seriously threatens human life and health. COPD The formation and development of the disease are determined by the internal genes and external environment. the combined effect of environmental factors. Tobacco smoke exposure combined with genetically engineered mice mimics the effects of specific genes under disease-causing conditions COPD biological effects. Check this article Research literature in recent years summarizes the application of the above methods in drug targets, inflammation and immunity. Applications of mechanism studies and their findings outline the research process of this approach. Should Written by COPD Provide reference for pathogenesis and drug research.
Keywords: Chronic obstructive pulmonary disease; Tobacco smoke; Genetically engineered mice; Purpose Genes; Pathology; Drug development

1 DRUG TARGET

Genetic engineering technologies include ES cell targeting technology, CRISPR With the improvement of gene editing technology, transgenic technology, etc., human beings ' ability to change genes is rapidly increasing. Currently, among genetically modified experimental animals, mice are most frequently used, and many models related to human diseases have been established[1]. COPD The formation and deterioration of the disease are determined by the joint action of internal genes and external environmental factors. As the main pathogenic factor, tobacco smoke exposure, combined with different transgenic mice, can elucidate the impact of changes in the expression of a specific gene on lung damage and key signaling pathways in animals exposed to tobacco smoke, and elucidate the role of specific genes or signaling pathways in COPD. role in pathological mechanisms and identify new drug targets. This article synthesizes and analyzes the research results of tobacco smoke exposure combined with genetically engineered mice on the pathological mechanisms and drug targets of COPD, and reports as follows.

1.1 Tristetraprolin (TTP)

TTP is composed of zinc finger protein 36 (zinc finger protein-36, ZFP36) A gene-encoded RNA-binding protein that binds to target cytokines through 3 '-Adenylate- and uridylate-rich polypeptide in the untranslated region The binding of these elements induces mRNA The destruction, especially the destruction of certain transcripts encoding inflammatory cytokines[2], may have a protective effect on COPD. The effect of TTP on reducing mRNA stability is regulated by phosphorylation and dephosphorylation of two specific residues, which in mice is phosphatidylserine 52 and 178, in humans is phosphatidylserine 60 and 186[3]. mitogen-activated protein kinase (MAPK) activated protein kinase 2 (MK2) Phosphorylation TTP, and make Of lose Live, guide To target mRNA of stable Determine[4]. protein phosphorus acid enzyme 2A (PP2A), dephosphorylate TTP, increase its activity, and promote target mRNA The stability is lost[5]. The activated TTP is targeted and degraded by the ubiquitin-proteasome system[5]. In these ways, the phosphorylation of the key phosphatidylserine controls the function of TTP. These phosphatidylserines act as a molecule to open Off: Phosphorylation, functionally closed, dephosphorylated, open. Therefore, if TTP is used as a new anti- COPD An anti-inflammatory target, it has the advantage of being easy to control. Nair et al.[5] used a genetically modified constitutively activated TTP mouse strain in which the phosphatidylserine 52 of the endogenous TTP protein and 178 Replaced by an alanine residue that cannot be phosphorylated (Zfp 36 aa/aa)[6]. These two amino groups Replacement of acid residues leads to structural activation of TTP and plays a role in destabilizing mRNA. Using Zfp 36 aa/aa mice to detect activated TTP for experimental tobacco smoke (cigarette smoke, CS) induce COPD Impact. Activated TTP found to be beneficial in experimental COPD Various characteristics of have a protective effect, Such as the reduction of pneumonia, reduction of airway remodeling, reduction of alveolar expansion and improvement of lung function. Subsequently in wild-type C57BL /6J In mice, use one kind PP2A exciting move agent (AAL(s)), to activate TTP, alone or in combination with the proteasome inhibitor borte - zomib, and subsequently evaluate the effect of these interventions on CS- induced experimental COPD Impact.

1.2 Advanced Glycation End Product Receptor (Receptor For Ad Vanced Glycation End Products, Rage)

Receptor for advanced glycation end products is a multiligand receptor. Tobacco smoke contains RAGE ligand has been Confirmed to be COPD one of the pathogens. Wild-type and RAGE knockout mice, respectively exposed to CS. After comparison, it was found that the lung group of RAGE knockout mice Tissue inflammatory lesions were significantly reduced, and the number of inflammation-related factors and neutrophils in the alveolar lavage fluid decreased. This result shows that knocking out RAGE can alleviate CS induced airwayitis disease. cDNA micro array ratio compare back hair present, make use way path Can able for S100A8/A9 Downregulation of expression and associated immune -Downregulation of inflammatory response[7]. Other have research study Knot fruit hair Now[8]: knock remove RAGE Gene or By answer The RAGE inhibitor FPS-ZM1 was used to prevent the progression of CS-induced emphysema in mice. exposure to CS knockout RAGE mice or C57BL /6 Unbiased gene expression profiling was performed on alveolar macrophages from wild-type mice and, by comparison, identified several genes essential for COPD pathogenesis, indicating that RAGE is involved in CS- induced macrophage activation. is a necessary component[8]. Two sources of fines cells, the most significant difference is Nrf 2 mediated gene expression. knockout RAGE mouse macrophages Nrf 2 Mediated gene expression and 4-hydroxynonenal in lung tissue (4-hydroxynonenal, 4 -HNE) decrease, indicating that in CS Lungs of knockout mice have lower levels of oxidative stress when stimulated. However, both mouse CS Same exposure, similar numbers of macrophages in alveolar lavage fluid, lung tissue CD 45 The percentages of positive expressing cells and neutrophil positive expressing cells are also similar[8], suggesting that CS- mediated oxidative stress may require RAGE. mediated by. In addition, in response to CS exposure, knockout mouse macrophages showed attenuation of endoplasmic reticulum stress[8]. These studies Studies have shown that the activation process of lung macrophages and lung injury process induced by CS , RAGE plays an important role; inhibits RAGE is New possible avenues for COPD treatment.

1.3 Senescent Cells

he senescence of cells is mediated by the Cdkn2a locus, which encodes two important tumor suppressors, named p16 Ink 4a and p19 Arf[9]. Hashimoto et al.[10] ablated Arf expressing cells, constructing an ARF - DTR transgenic mouse and improving the lung function of the mice. Preemption of Arf with diphtheria toxin Expressing cells can reduce elastase-induced lung damage and produce a certain protective effect on lung tissue[11]. Further research found: long-term Tobacco smoke exposure leads to abnormal lung function, abnormal lung morphology and structure, and aging signature proteins Ink 4a and Arf Increased expression in lung tissue; upon tobacco smoke exposure Before, elimination of Arf- expressing cells alleviated the above smoke-induced phenotypic changes. Additionally found: Elimination of Arf- expressing cells after lung injury also had beneficial effects in mice challenged with tobacco smoke extract; preliminary findings It was found that the protective effect of clearing senescent cells is related to the reduced production or activity of elastase secreted by macrophages[12]. These results suggest that aging cells Cells are an important therapeutic target for COPD.

2 INFLAMMATION AND IMMUNE RESPONSE

2.1 Normal Lung and Inflamed Lung

Normal lung and inflamed lung for CS stimulus-response ratio Compare, yes At reason untie COPD shape become and hair exhibition yes have beneficial. β ENaC mouse, a transgenic overexpressing Scn n1b In mice, the gene encodes live lies in gas Taoist superior Thin skin cellular Na + Pass Dao β Asia one Bit (β ENaC). β ENaC mice have dehydrated airway mucus and spontaneously develop chronic bronchitis and emphysema, including mucus cell metaplasia, mucus hypersecretion, mild neutrophilic inflammation, large foamy macrophages, and airway inflammation. The number of lymphocytes in the airway mucus and airway wall increases[13]. Engle et al.[14] used wild mice and β ENaC chronic pneumonia mice, exposed to CS or control air, respectively exposed to 1 d and 5 d. In lung tissue or alveolar lavage fluid, control The number of white blood cells, neutrophils, macrophages, and lymphocytes in β ENaC mice was higher than that in control or CS wild mice, reflecting the spontaneous lung tissue inflammation in β ENaC mice. Mild inflammation occurs in the lungs of wild-type mice after CS stimulation reaction. and β ENaC control comparison, CS exposed There were no significant changes in the number of white blood cells, macrophages, and lymphocytes in β EN aC mice ; however, the number of neutrophils, despite exposure 1 d, no difference; but at exposure 5 d later, the β ENaC group exposed to CS significantly decreased. Both models show: exposure 1 d Changes in inflammatory mediators compared with exposure 5 d The medium changes, the amount of change More. Transcriptomic results show: Exposure 1 d or 5 d, wild or βENaC Many genes and gene sets in mice respond similarly, such as genes related to oxidative stress. Immune response genes are downregulated due to upregulation. Only a few genes regulate and produce There are differences in chemical reactions: Compared with the control air exposure group, the smoke exposure group Extracellular matrix-related genes and gene sets, in Exposure 1 d is upregulated, but in 5 ddownregulation. Taken together, these results indicate that lung gene expression changes rapidly after a single smoke exposure, and repeated short-term exposure does not significantly change gene expression. changes; in lung tissue where inflammation has already occurred, by downregulating certain inflammatory reactions It has a certain protective effect against repeated subsequent smoke irritation damage. Should The results support the hypothesis that in response to smoke stimulation, early lung tissue rapidly generates Some reactions have a protective effect against repetitive lung injury[14]. This hypothesis starts from To some extent, it explains that smokers need many years of smoking history, long-term and continuous Smoke stimulation may cause airway and alveolar lesions, and ultimately form COPD.

2.2 Secondary Immune Response Cells

Exist COPD In pulmonary tissue, secondary An increase in the number of sexual immune response cells, mainly infiltrating CD 4+ T, CD8 + T and B lymph thin cells. CD8 + T No enough mouse (CD8-/-),and No It's CD 4 + T-deficient mice, for CS- induced lung injury with certain resistance properties, specifically preventing the accumulation of macrophages, MMP2 and MMP9 activation and emphysema[15], indicating that in the pathological mechanism of the disease, CD 8 + T Cells played a role some key role. Lack of mature T cells compared with wild-type controls and B cell(Rag2-/-) mice showed no changes in inflammation and emphysema transformation[16]. However, from Adoptive delivery of CD 3 in CS- exposed wild-type mice + T thin cell to Rag2-/- mice, which form a similar COPD performance, description in COPD In the formation and development of pathogenic T cells, there are certain key effect. long-term exposure to CS Wild-type mice with Rag 1-/- mice, pneumonia and lung function did not differ, but Rag 1-/- Collagen deposition in mouse airways is more severe Heavy, IL -33, IL -13 as well as ILC 2 The number also increases; illustrated in experimental COPD Medium, T/B lymphocytes play a role in airway collagen deposition and fibrosis. effect, but has no effect in inflammation[17].

2.3 2 Innate Lymphocyte Type

2 type innate lymphocytes (group 2 innate lymphoid cells, ILC2s), in communicating the innate immune response and secondary immunity It plays an important role in response and maintaining the homeostasis of the lung environment[18]. IL - Cs cells are tissue-resident lymphocytes. Depending on different stimuli, these cells Cells show plasticity[19]. in COPD In, use IL -1β, IL-4 and IL-12 wait Stimulus, ILC 2s Phenotypic transformation occurs, forming ILC 1s cell or ILC 3S thin cells; ILC 1S: ILC 2S There is a relationship between an increase in the ratio and a decrease in lung function and disease severity. exist straight Received Mutually close Sex[19]. ILC2 No enough change Gene Rora fl/fl II 7 r Cre Mice versus wild-type mice, long-term administration CS exposed despite Rora fl/fl II 7 r Cre mice have reduced emphysema, but collagen deposition and IL -33 and IL -13 The expression has not improved[17]. These studies suggest that ILC 2s cells Experimental COPD In CS-induced airway remodeling and emphysema, a It has a certain protective effect but has no effect on inflammation.

2.4 DNER /Notch Path

Exist COPD In clinical studies, whole genes group association(genome-wide association studies, GWAS) method got Widely used, it has become a powerful tool to obtain candidate genes or gene regions associated with target traits[20]. Applying this technology, Busch[21] found that the airway of smokers Epithelial DNER(Delta Notch like epidermal growth factor related receptor, DNER) in the district one indivual one nuclear Glycoside acid many state sex(SNP) and FEV1/FVC Compare Rate or FEV1 between, save exist most show Living Mutually close sex; with COPD There is also an association between genetic risk.

DNER is a transmembrane protein that belongs to the non-classical Notch ligand family. Its outer membrane segment is Notch 1 Receptor binding in a manner independent of CSL (CBF 1 Suppressor of Hairless, La g-1) way, activation Notch path. In human lung tissue, DNER is the main phenotype of pro-inflammatory macrophages[22]. through should Using DNER genetically engineered mice, combined with tobacco smoke exposure, further elucidated DNER/The mechanism of action of the Notch pathway:

giant lung tissue was found in tobacco smoke-exposed wild-type mice. Elevated DNER expression on phagocytes was followed by the discovery that pro-inflammatory M1 bone marrow-derived macrophages cell(M1 bone marrow derived macrophages, M1B MDM) DNER The expression increases[23]. Subsequent studies selected a DNER knockout of small mouse, no knockouts found DNER It has an impact on the polarization of macrophages, and it is speculated that DNER plays a role in M1 BMDM The high expression may be exerted by regulating signaling pathways Function[23]. Using gene set enrichment analysis (Gen e set enrichment analysis, GSEA) Comparing M1BMDM of wild-type mice and DNER knockout mice, it was found that interferon (interferon, IFN) The signaling pathway is most enriched in wild mice, and the difference between the two is obvious, which may reflect the presence of IFN in M1BMDM of DNER knockout mice. Damage or deficiencies in signaling pathways. Then it was discovered that knockout DNER mouse M1 BMDM thin cells receive prick exciting After, II dry type disturb white(type II interferon, IFNγ) -induced expression is significantly reduced; GESA shows M1 IFNγ signal enrichment, Low in knockout mice and high in wild-type mice. Although T Cells are IFNγ The main thing comes Source, Ran That's all through point ized wild born mouse T thin cells Asia group surface reach very Low DNER, Prompt T cells DNER It is impossible to regulate the production of large amounts of IFNγ ; Therefore, high expression of DNER M1 Macrophages are responsible for the high expression of IFNγ Reason[23]. In subsequent in vivo experiments, wild-type mice and knockout DNER mice were exposed to CS separately, and the results found that: in M1 In macrophages, DNER table Da is activated; IFNγ increase, need DNER expression; In chronic inflammation, DNER regulates IFNγ secretion by macrophages ; IFNγ production The macrophages belong to Recruited rather than resident macrophages; macrophages recruited in the lungs Intracellular, DNER regulated IFNγ secretion. Knockout was finally discovered DNER mouse In macrophages, NICD 1 Nuclear translocation was significantly reduced; two mouse macrophages Cellular GSEA In comparison, the Notch1 signaling pathway in wild mice is more enriched. according to This idea: with the help of DNER, CS induces Notch 1 in lung macrophages in vivo Letter Activation of signaling pathway subsequently induces high expression of IFNγ.

3 SUMMARY AND OUTLOOK

Currently, COPD Individualized treatment has become a consensus, and individual genetic differences It is often an important factor leading to different clinical phenotypes of COPD[2 4]. individualize The nature of treatment should reflect the complex and complex nature of COPD genotypes in causative conditions. Rich diversity of changes.

With the development of molecular biology, bioinformatics and other technologies, people have More and more COPD phenotypes and their specific genes have been identified, and established A more mature research model. First, pass GWAS Skills Using this technique to detect normal people and COPD patients, we found genes and genes with highly differential expression. Because of the seat, as a potential COPD Susceptibility genes and loci. Then, choose to change Mice modified with a certain gene to be screened and wild mice used as controls were given tobacco smoke stimulation respectively, and the changes in important COPD indicators between the two were compared ; in addition, it should be Use agonists or antagonists to interfere with the expression of this gene in COPD wild mice to once again verify whether this gene is related to COPD. related to the occurrence and development of. This mode, In studies exploring the pathogenesis of COPD and drug intervention targets, it has been application and achieved certain progress.

In the future, research models combining tobacco smoke exposure with genetically engineered mice will Promote the accurate identification of complex phenotypes of COPD and promote changes in different target genes Establishment and improvement of COPD model system in mice combined with tobacco smoke exposure, promotion The establishment and development of individualized treatment of animal COPD.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

REFERENCES

[1] Liu Di, Zhang Hongchun. Research progress on genetically engineered animal models of chronic obstructive pulmonary disease Exhibition. Chinese Journal of Bioengineering, 2020, 40(4): 59-6 8.

[1] Liu D, Zhang H C. Advances in genetically engineered animal models of chronic obstructive pulmonary disease. Chin Biotechnol, 2020, 40(4): 59-68.

[2] Brooks S A, Blackshear P J. Tristetraprolin (TTP): interactions with mRNA and proteins, and current thoughts on mechanisms of action. Biochim Biophys Acta, 2013, 1829(6-7): 666-79.

[3] Clark A R, Dean J L. The control of inflammation via the phospho- rylation and dephosphorylation of tristetraprolin: a tale of two phosphatases. Biochem Soc Trans, 2016, 44(5): 1321-37.

[4] Chrestensen C A, Schroeder M J, Shabanowitz J, et al. MAPKAP kinase 2 phosphorylates tristetraprolin on in vivo sites including Ser178, a site required for 14-3-3binding. J Biol Chem, 2004, 279(11): 10176-84.

[5] Nair P M, Starkey M R, Haw T J, et al. Enhancing tristetraprolin activity reduces the severity of cigarette smoke-induced experimental chronic obstructive pulmonary disease. Clin Transl Immunology, 2019, 8(10): e01084.

[6] Ross E A, Smallie T, Ding Q, et al. Dominant suppression of in- flammation via targeted mutation of the mRNA destabilizing protein Tristetraprolin. J Immunol, 2015, 195(1): 265-76.

[7] Chen M, Wang T, Shen Y, et al. Knockout of RAGE ameliorates mainstream cigarette smoke-induced airway inflammation in mice. Int Immunopharmacol, 2017, 50: 230-5.

[8] Sanders K A, Delker D A, Hueckstead T, et al. RAGE is a criti- cal mediator of pulmonary oxidative stress, alveolar macrophage ac- tivation and emphysema in response to cigarette smoke. Sci Rep, 2019, 9(1): 231.

[9] Ben-Porath I, Weinberg R A. The signals and pathways activating cellular senescence. Int J Biochem Cell Biol, 2005, 37 (5): 961-76.

[10] Hashimoto M, Asai A, Kawagishi H, et al. Elimination of p19ARF - expressing cells enhances pulmonary function in mice. JCI In- sight, 2016, 1(12): e87732.

[11] Mikawa R, Suzuki Y, Baskoro H, et al. Elimination of p19ARF -ex- pressing cells protects against pulmonary emphysema in mice. Aging Cell, 2018, 17(5): e12827.

[12] Mikawa R, Sato T,Suzuki Y,et to lp19 ARF exacerbates cigarette smoke-induced pulmonary dysfunction, J Biomolecules,2020,1 (3): 462.

[13] Saini Y, Dang H, Livraghi-Butrico A, et al. Gene expression in whole lung and pulmonary macrophages reflects the dynamic pathol- ogy associated with airway surface dehydration. BMC Genom- ics, 2014, 15(1): 726.

[14] Engle M L, Monk J N, Jania C M, et al. Dynamic changes in lung responses after single and repeated exposures to cigarette smoke in mice. PLoS One, 2019, 14(2): e0212866.

[15] Maeno T, Houghton A M, Quintero P A, et al. CD8 + T cells are required for inflammation and destruction in cigarette smoke-in-duced emphysema in mice. J Immunol, 2007, 178(12): 8090 - 6.

[16] Motz G T, Eppert B L, Wesselkamper S C, et al. Chronic cigarette smoke exposure generates pathogenic T cells capable of driving- COPD-like disease in Rag2/mice. Am J Respir Crit Care Med, 2010, 181(11): 1223-33.

[17] Donovan C, Starkey M R, Kim R Y, et al. Roles for T/B lympho- cytes and ILC2s in experimental chronic obstructive pulmonary dis- ease. J Leukoc Biol, 2019, 105(1): 143-50.

[18] Monticelli L A, Buck M D, Flamar A L, et al. Arginase 1 is an innate lymphoid-cell-intrinsic metabolic checkpoint controlling type 2 inflammation. Nat Immunol, 2016, 17(6): 656-65.

[19] Silver J S, Kearley J, Copenhaver A M, et al. Inflammatory triggers associated with exacerbations of COPD orchestrate plasticity of group 2 innate lymphoid cells in the lungs. Nat Immunol, 2016, 17(6): 626-35.
[20] Silverman E K. Genetics of COPD. Annu Rev Physiol, 2020, 82: 413-31.
[21] Busch R, Hobbs B D, Zhou J, et al. Genetic association and risk scores in a chronic obstructive pulmonary disease meta-analysis of 16, 707 subjects. Am J Respir Cell Mol Biol, 2017, 57(1): 35 - 46.
[22] D 'Souza B, Meloty-Kapella L, Weinmaster G. Canonical and non- canonical Notch ligands. Curr Top Dev Biol, 2010, 92: 73 - 129.
[23] Ballester-López C, Conlon T M, Ertüz Z, et al. The Notch ligand DNER regulates macrophage IFNγ release in chronic obstructive pulmonary disease. EBiomedicine, 2019, 43: 562-75.
[24] Singh D, Agusti A, Anzueto A, et al. Global strategy for the diag- nosis, management, and prevention of chronic obstructive lung dis- ease: the GOLD science committee report 2019. Eur Respir J, 2019, 53(5): 1900164.