World Journal of Methodology

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DOI: 10.5662/wjm.v5.i4.223

World J Methodol 2015 December 26; 5(4): 223-229
ISSN 2222-0682 (online)

MINIREVIEWS

Forkhead box protein A2 and T helper type 2-mediated pulmonary inflammation

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Author contributions: Sun L and Tang XJ generated the figures and wrote the manuscript; Luo FM designed the aim of the editorial and wrote the manuscript.

Supported by The National Natural Science Foundation of China, Nos. 30871118, 30971325, 81270129 and 81470268 (FL); and grants from Department of Science and Technology of Sichuan Province, Nos. 09ZQ026-020 and 2009SZ0190 (FL).

Conflict-of-interest statement: None.

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Received: January 29, 2015
Peer-review started: January 30, 2015
First decision: March 6, 2015
Revised: March 24, 2015
Accepted: September 29, 2015

Article in press: September 30, 2015
Published online: December 26, 2015

Abstract

The transcription factor forkhead box protein A2 (FOXA2, also known as hepatocyte nuclear factor 3β or transcription factor 3β), has been found to play pivotal roles in multiple phases of mammalian life, from the early development to the organofaction, and subsequently in homeostasis and metabolism in the adult. In the embryonic development period, FOXA2 is require d for the formation of the primitive node and notochord, and its absence results in embryonic lethality. Moreover, FOXA2 plays an important role not only in lung development, but also in T helper type 2 (Th2)-mediated pulmonary inflammation and goblet cell hyperplasia. In this article, the role of FOXA2 in lung development and Th2-mediated pulmonary inflammation, as well as in goblet cell hyperplasia, is reviewed. FOXA2 deletion in airway epithelium results into Th2-mediated pulmonary inflammation and goblet cell hyperplasia in developing lung. Leukotriene pathway and signal transducers and activators of transcription 6 pathway may mediate this inflammation through recruitment and activation of denditric cell during lung developments. FOXA2 is a potential treatment target for lung diseases with Th2 inflammation and goblet cell hyperplasia, such as asthma and chronic obstructive pulmonary disease.

Key words: Forkhead box protein A2; T helper type 2 inflammation; Pulmonary; Development; Goblet cell hyperplasia

Core tip: The transcription factor forkhead box protein A2 (FOXA2) plays pivotal roles in embryonic development and

organogenesis. Conditional deletion of FOXA2 in airway epithelial cells during the early stage of lung development will result in abnormal morphology of the lung and T helper type 2-mediated pulmonary inflammation. In addition, FOXA2 regulates the goblet cell differentiation during lung development and in pulmonary diseases such as asthma and chronic obstructive pulmonary disease. FOXA2 may be a new target for the treatment of lung disease.

Sun L, Tang XJ, Luo FM. Forkhead box protein A2 and T helper type 2-mediated pulmonary inflammation. *World J Methodol* 2015; 5(4): 223-229 Available from: URL: http://www.wjgnet.com/2222-0682/full/v5/i4/223.htm DOI: http://dx.doi.org/10.5662/wjm.v5.i4.223

INTRODUCTION

The transcription factor forkhead box protein A2 (FOXA2), also known as hepatocyte nuclear factor 3β (HNF3β), is first identified by its ability to regulate liver-specific gene expression[1]. FOXA2 is a part of the large Forkhead box (*FOX*) gene family that all members have the DNA binding "winged helix domain"[2]. The gene of *FOXA2* is located in chromosome 20p11.21. FOXA2 is able to bind to specific DNA sequence[3], activate or inhibit the transcriptional activity of target genes, and also participate in cellular signal transduction[4] and metabolism regulation[5]. Meanwhile, it plays a key role in the development[6] and mature of tissues and organs[7].

With the development of mouse embryos, the first active *FOXA* gene is FOXA2 whose RNA and protein are detected on day 6.5 of gestation in the primitive streak and node[8], suggesting that FOXA2 plays an essential role in the formation of the primitive streak and endoderm[9]. The research has indicated that FOXA2 is required for the maintenance of dopaminergic properties in ventral midbrain neurons at late embryonic stage[10]. The expression of FOXA2 is also found in the liver, pancreas, lung, intestine, thyroid gland and prostate[11], implying that FOXA2 not only regulates the organogenesis and development of liver[7,12,13] and lung[14,15], but also participates in the process of glucose[16] and lipid metabolism[17]. Many studies have also shown that FOXA2 has a close relationship with the occurrence and metastasis of tumor[18-20]. For the past few years, FOXA2 is found to participate in regulating the lung development, Th2-mediated pulmonary inflammation and goblet cell hyperplasia[21,22].

STRUCTURE OF FOXA2

FOXA2 gene is located in chromosome 20p11.21 and its length is 2242 bp. As a member of the FOXA family, FOXA2 has a forkhead domain (FHD) complexed to a target DNA. The first 3D structure of FHD resolved by X-ray crystallography was that of FOXA3/HNF3γ in 1993[3]. Subsequently, the FHD structures of other members were resolved, which are similar to that of FOXA3[23], so is FOXA2. The FHD contains three N-terminal α-helices (H1-3), three β-strands and two loops (W1-2) towards its C-terminal region[24]. The recent data about the FOXA function have identified the FOXA proteins as "pioneer factors" whose binding to promoters and enhancers enable chromatin access for other factors[25-27]. It is unique in that FOXA2 is the only one in the family which contains an AKT2/PKB phosphorylation site at the N terminus of the FHD[27]. FOXA2 has two nuclear localization sequences (NLS) which are located at both ends of the FHD[28], one of the two NLS in H1 while the other in W2[24] (Figure 1).

ROLE OF FOXA2 IN DEVELOPMENT

Research has shown that the FOX superfamily express in many kinds of organism from invertebrate to vertebrate and its subfamily FOXA participants in the whole process of the embryonic development[29]. FOXA2, a member of FOXA family, is the first gene of this family to be expressed in the progress of embryogenesis[30]. In the study of mouse embryogenesis, the expression of the *FOXA2* gene appears first at the anterior of the primitive streak. After the primitive node has formed, FOXA2 expression is localized in the primitive node, notochord and neural plate[31]. Mice lacking FOXA2 die by E10 to E11 and show marked defects in structures related to embryogenesis, without forming a distinct primitive node, aberrant somites and neural tube resulting from the absence of the notochord, and failure to form the gut tube, although endoderm cells are present[6]. The defects of the notochord and neural tube, can be ascribed to a deficiency of Sonic hedgehog, as FOXA2 cooperates with the homeobox gene Goosecoid in the activation of this gene[32]. Furthermore, FOXA2 can activate the canonical WNT-β-catenin pathway and subsequently induce the primitive extraembryonic endoderm by directly up-regulating the Wnt6[33].

With the embryonic development, the expression of *FOXA2* is also detected in definitive endoderm and endoderm-derived apparatus such as liver, pancreas, and prostatic gland, where it persists through development to adulthood[30,31,33-36]. As to the lung, *FOXA2* expresses in the endoderm which later differentiates into the lung buds, where it expresses continuously in the pulmonary epithelium to adulthood[37]. *FOXA2* is found in specific subsets of respiratory epithelial cells. In the respiratory epithelium, *FOXA2* can activate the transcription of thyroid transcription factor-1 (TTF-1), clara cell secretary protein and surfactant proteins (A-D), which mark the differentiation of epithelial cells[38,39]. Moreover, the surfactant proteins A-D play critical roles in surfactant function and homeostasis[40]. In the mice lacking *FOXA2* in conducting airways, pulmonary abnormalities are not observed by light microscopy at E18.5. However, the decreased alveolar septation and peripheral saccules appear at PN3. At PN15 and later, pulmonary

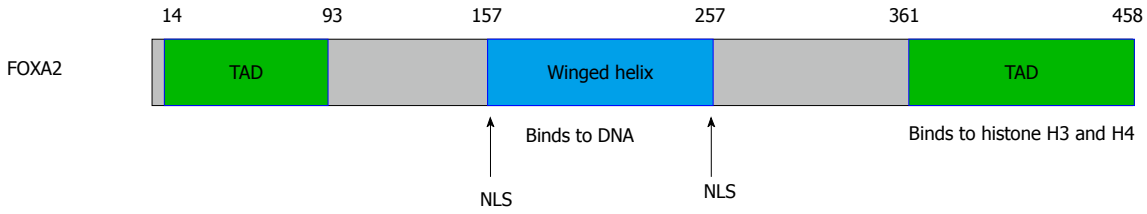

Figure 1 Structure of forkhead box protein A2 protein. FOXA2 has two transactivation domains and two nuclear localization sequences. There is a winged helix in the central of FOXA2. FOXA: Forkhead box protein A; TAD: Transcription activation domain; NLS: Nuclear localization sequences.

abnormalities including emphysema in distal airways and goblet cell hyperplasia in bronchi and bronchioles are observed in the FOXA2$^{\Delta/\Delta}$ mice[15,41]. *FOXA2* is indeed a positive regulator for E-cadherin gene[42], a cell adhesion molecule required for normal lung branching morphogenesis and cell differentiation[43,44]. Mildred *et al*[45] verified that the temporal-spatial expression patterns of *FOXA2* in the developing and regenerating of lung fit in with their proposed function in epithelial cell differentiation and regeneration, and surfactant protein gene expression. In summary, *FOXA2* plays a critical role in the development of lung.

ROLE OF FOXA2 IN TH2-MEDIATED PULMONARY INFLAMMATION AND GOBLET CELL HYPERPLASIA

Evidences showed that respiratory epithelial cells lining conducting airways regulate the inflammatory responses caused by allergens, pathogens and injurious agents[46,47]. Disruption of FOXA2 in respiratory epithelial cells results in airspace enlargement, neutrophilic pulmonary infiltrates, mucus hypersecretion, goblet cell hyperplasia and metaplasia (GCHM)[15], associated with the activation of pro-GCHM Stat6 and epidermal growth factor receptor signaling pathways[15,21,48]. Further study demonstrates that lack of FOXA2 in airway epithelial cells results in Th2-mediated pulmonary inflammation, including infiltration of eosinophiles, up-regulation of Th2 cytokines and chemokines, goblet cell hyperplasia and mucus hypersecretion, accompanied by the activation of leukotriene pathway at PN15[21]. All these findings are common in the lung of asthma patients. Therefore, FOXA2 expression in the lung may be disturbed in asthma. In fact, decreased expression of FOXA2 in the lung is found in asthma patients compared with control subjects[49]. The decreased expression of FOXA2 was negatively correlated with increased expression of mucin-5ac (MUC5ac) and chloride channel accessory 1[49]. Furthermore, the expression of FOXA2 in airway epithelial cell is inhibited by allergen challenge, and by over-expression of Th2 cytokines such as interleukin (IL)-4 and IL-13 in mouse airway epithelium[15], and also by IL-13 stimulation in human bronchial epithelial cells[48]. All these results indicate that FOXA2 plays a critical role in Th2-mediated pulmonary inflammation in developing lung. Although it inhibits goblet cell hyperplasia and metaplasia, conditional over-expression of FOXA2 in the respiratory epithelium in adult mice prior to ovalbumin (OVA) sensitization cannot alter Th2 cytokine production or inflammation in the lung[21]. Inflammatory cell counts, as well as IL-4, IL-5, IL-13, IL-10, and interferon-γ concentrations, are similar in bronchoalveolar lavage fluid (BALF) from FOXA2 over-expressing and control mice after OVA exposure[21]. Tang *et al*[22] also demonstrate that in the very early stage (from PN0 to PN10) of lung development after birth, Th2-mediated inflammation is missing in the lung of mice with FOXA2 deletion in airway epithelium. The Th2 related cytokines and chemokines are up-regulated from PN7 and Th2 inflammation in the lung is obvious on PN15. All the results indicate that Th2-mediated pulmonary inflammation induced by deletion of FOXA2 in airway epithelial cells is development-depended.

MECHANISM OF FOXA2 REGULATING TH2-MEDIATED PULMONARY INFLAMMATION AND GOBLET CELL HYPERPLASIA

The mechanism of Th2-mediated pulmonary inflammation induced by deletion of FOXA2 in airway epithelial cells remains unknown at present. Dendritic cell (DC) plays a very important role in Th2-mediated pulmonary inflammation. Chen *et al*[21] investigates the role of myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) in this inflammation. They found that the frequency of both DCs and mDC/pDC ratio are significant increased in the lung of *FOXA2*$^{\Delta/\Delta}$ mice[21]. They also found that frequencies of mDCs expressing B7-DC, B7-H1, and CD86 are significantly elevated[21]. The results indicate that increased recruitment and activation of pulmonary mDCs may mediate the Th2 inflammation in the lung in *FOXA2*$^{\Delta/\Delta}$ mice during development. However, the mechanism of the recruitment and activation of pulmonary mDCs after FOXA2 deletion in airway epithelial cells is not clear. Previous studies have provided direct evidence that cysteinyl leukotrienes (cys-LTs) plays an important role in regulating Th2 cell-dependent pulmonary inflammation[50,51]. Further study discloses that FOXA2 regulates 15-lipoxygenase (Alox15) and Alox5 gene transcription associating with leukotrienes (LTs) biosynthesis and lung inflammation[52,53]. Montelukast,

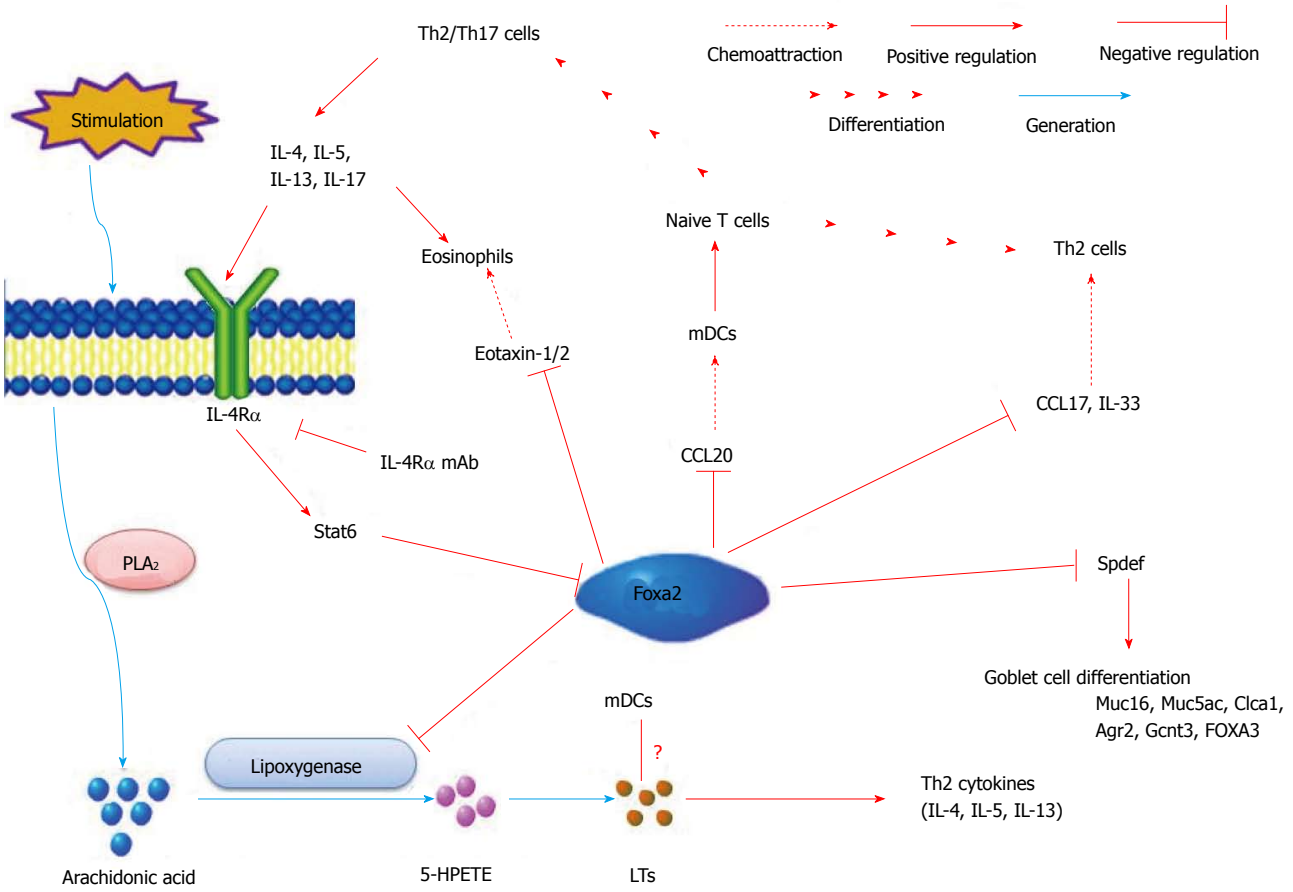

Figure 2 Network of forkhead box protein A2 regulating T helper type 2 inflammation and goblet cell hyperplasia. IL: Interleukin; mDC: Myeloid dendritic cell; CCL: Chemokine (C-C motif) ligand; Stat6: Signal transducers and activators of transcription 6; PLA2: Phosolipase A2; HPETE: Hydroperoxyeicosatetraenoic acid; LTs: Leukotrienes; MUC: Mucin; FOXA: Forkhead box protein A; Gcnt3: Glucosaminyl (N-Acetyl) transferase 3.

a selective inhibitor of the CysLT$_1$ receptor[54,55], suppresses the Th2-mediated inflammation arising from the ablation of FOXA2 in the developing mice lung. In developing FOXA2$^{\Delta/\Delta}$ mice, the increased expression of Th2 cytokines followed the activation of LT pathway. In brief, these findings uncover that FOXA2 is required for the repression of Th2-mediated pulmonary inflammation during lung development *via* its regulation to CysLT pathway[22]. Therefore, deletion of FOXA2 in the early stage of lung development leads to the spontaneous activation of LTs pathway. The activated LTs pathway may increase the recruitment and activation of pulmonary mDCs and then mediate the Th2 inflammation in the lung of *FOXA2*$^{\Delta/\Delta}$ mice during development. However, this hypothesis needs more direct evidences (Figure 2).

IL-13/IL-4-STAT6 pathway plays a critical role in Th2-mediated pulmonary inflammation[56,57]. Chen *et al*[21] tests whether Th2-mediated pulmonary inflammation and goblet cell differentiation caused by conditional deletion of FOXA2 in the airway epithelium is depend upon IL-4R–mediated signaling. The results indicate that administration of IL-4Rα mAb, an antibody which blocks IL-4Rα (a key molecular in IL-13/IL-4-STAT6 signaling pathway), significantly inhibits eosinophilic inflammation and goblet cell metaplasia and mucus hyper-production in *FOXA2*$^{\Delta/\Delta}$ mice. These results indicates that IL-4Rα-STAT6 pathway mediated the Th2 pulmonary inflammation and goblet cell hyperplasia in *FOXA2*$^{\Delta/\Delta}$ mice during lung development[21]. Wan *et al*[15] found that intratracheal administration IL-4 resulted in the decrease expression of FOXA2 and this effect is STAT6-depended. However, over-expression of FOXA2 in airway epithelium of adult mice inhibis goblet cell metaplasia and mucus hyper-production caused by OVA, but not Th2-mediated pulmonary inflammation[21]. These results indicate that the interaction between FOXA2 and IL-13/IL-4-STAT6 signaling pathway may be reciprocal in Th2-mediated inflammation and goblet cell hyperplasia in the lung.

REGULATION OF *FOXA2* EXPRESSION

FOXA2 in airway epithelial cells plays important role in lung development and Th2-mediated pulmonary inflammation, as well as in goblet cell hyperplasia. Therefore, regulation of *FOXA2* expression in airway epithelial cells may have potential role in the pathogenesis and treatment of lung diseases, such as asthma and chronic

obstructive pulmonary disease (COPD). Unfortunately, No medicine up-regulating *FOXA2* expression has been investigated in animal model or patients with COPD and asthma. Recent study indicated that Tetrapeptide Ala-Asp-Glu-Leu, a peptide which is effective on models of acute bacterial lung inflammation, fibrosis, and toxic lung damage, could increase the expression of *FOXA2* and decrease expression of MUC5ac in cultured bronchial epithelium[58]. Whether this peptide has the same effect *in vivo* has not been tested yet.

Thioredoxin-interacting protein (TXNIP) increases the expression of human islet amyloid polypeptide (IAPP) in beta-cell. TXNIP-induced FOXA2 transcription factor expression is conferring this effect by promoting FOXA2 enrichment at the proximal FOXA2 site in the IAPP promoter[59]. TXNIP can down-regulate miR-124a expression, which can directly target FOXA2. Indeed, miR-124a overexpression led to decreased FOXA2 expression and also can be effectively inhibited by TXNIP[59]. Thus, this study identifies a novel TXNIP/miR-124a/FOXA2/IAPP signaling cascade linking the critical beta-cell signaling pathway. However, whether this pathway also plays a role in airway epithelial cells and thus regulates the goblet cell hyperplasia and mucus production remains unknown.

Recent study demonstrates that over expression of NK2 homeobox 1 (NKX2-1, also known as TTF-1), inhibits allergen-induced goblet cell hyperplasia and airway inflammation[60]. Further study indicates that loss of FOXA2 in airway epithelial cell is prevented by over expression of NKX2-1 at the same time[60]. All these results suggest that NKX2-1 may regulate the FOXA2 expression in airway epithelial cell.

CONCLUSION

In conclusion, as a member of the FOX superfamily, FOXA2 participates in the formation and development of organs. Meanwhile, FOXA2 plays a very important role in lung development, Th2-mediated pulmonary inflammation and goblet cell hyperplasia. Lose of FOXA2 in the early stage of lung development will result in abnormal morphology of the lung and Th2-mediated pulmonary inflammation. FOXA2 regulates the goblet cell differentiation during lung development and in pulmonary diseases such as asthma and COPD. LTs pathway and STAT6 pathway which are regulated by FOXA2 mediate the Th2 pulmonary inflammation and goblet cell hyperplasia. Moreover, other transcription factors, such as NXK-2-1, may cooperate with FOXA2 in lung development, Th2-mediated pulmonary inflammation, and also in lung diseases with goblet cell hyperplasia.

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