



GATA-3 (GATA BINDING PROTEIN 3) MOLECULAR TARGET FOR ASTHMA AND ALLERGIC DISORDER REVIEW ARTICLE

Navneet Om Prakash Soni*

Department of Pharmacology, Prakash Institute of Medical Science, Islampur, Sangli, Maharashtra, India.

ABSTRACT

Article highlight History , Structure ,Function ,Role of GATA-3 in Th2 differentiation study supporting the role of GATA-3 in allergic and airway disorder (Asthma) and targeting GATA-3 in treatment of Asthma.

Key words: Th1, Th2, GATA3, Asthma, IL 4, IL5.

INTRODUCTION

GATA-3 is one such master regulator of cellular fate, which was identified in 1990 along with Two other GATA family members and was found to be abundantly expressed in T lymphocytes and the brain (Yamamoto M *et al.*, 1990).

GATA-3 is the main GATA family member that is expressed in immune cells and can be easily detected in developing and mature T cells, natural killer (NK) cells, and CD1-restricted natural killer T (NKT) cells.

GATA-3 as transcription factor

GATA-3 was first described as a transcription factor that interacts with the TCR- α gene enhancer (Ho IC *et al.*, 1991).

Family members

The mammalian GATA family of transcription factors consists of six members:

GATA-binding protein 1 (GATA-1)–GATA-6. These proteins are highly homologous, conserved among species, have distinctive tissue-specific expression patterns, and play essential roles during vertebrate development.

Classification

Based on their profile of tissue-specific expression, the GATA proteins can be classified as

- A) Hematopoietic (GATA-1–GATA-3)
- B) Nonhematopoietic (GATA-4–GATA-6) (Hosoya T *et al.*, 2010)

Distribution

GATA-1 and GATA-2 that are primarily expressed in hematopoietic cells. GATA-4, -5, and -6 whose expression is restricted to mesoderm- and endoderm-derived tissues, such as the heart, liver, and intestines. GATA-3 is present in both hematopoietic (e.g., T cells) and non-hematopoietic tissues

OTHER SITE OF EXPRESSION GATA-3

GATA-3 mRNA is also expressed in the multipotent progenitors (MPPs) and at the pre-pro-B cell stage in the bone marrow. GATA-3 is expressed in many embryonic and adult tissues, including the adrenal glands, kidneys, central nervous system, inner ear, hair follicles, skin and breast tissue (mammary glands), and important functions for GATA-3 in several of these tissues have been shown in knockout and conditional knockout mouse models (Hosoya T *et al.*, 2010).

CLONING OF GATA 3

The laboratory of Engel was the first to clone the GATA-3 gene and further dissected Important biochemical properties of the GATA-3 protein (George KM *et al.*, 1994).

Corresponding Author

Navneet Om Prakash Soni

Email: navneetsoni1978@yahoo.com

STRUCTURE OF GATA 3

GATA-3 contains a distinct amino-terminal region that contains two trans-activation domains followed by two highly conserved zinc-finger domains in which the C-terminal finger and the immediately adjacent conserved basic region together constitute the DNA-binding domain (Hosoya T *et al.*, 2010).

GATA family of transcription factors that are conserved proteins containing one or two C2-C2-type zinc fingers and a highly conserved C4 zinc finger that recognizes a consensus DNA sequence A/TGATAA/G from which the name of the family originated (Hosoya T *et al.*, 2010).

GATA-3 SIGNAL

For GATA-3 to regulate gene expression, it must translocate from the cytoplasm into the nucleus to access its target genes. GATA-3 contains a classical nuclear import signal, and is transported into the nucleus by importin- α . The affinity of GATA-3 to importin- α is regulated by phosphorylation, which is mediated by p38 mitogen-activated protein kinase (MAPK) (Maneechotesuwan K *et al.*, 2009).

Half life –short half life 1 hour

Degradation

GATA-3 is ubiquitinated in vitro and in vivo and degraded by the 26s proteasome pathway.

GATA-3 IN HUMAN EMBRYOS

In human embryos, GATA-3 expression can be detected from the beginning of the fourth week of gestation (Debacker C *et al.*, 1998).

MUTATION IN GATA-3

Barakat syndrome in humans, characterized by familial hypoparathyroidism, sensorineural deafness, and renal dysplasia (also known as HDR syndrome)

FUNCTION OF GATA-3

GATA-3 is a critical regulator in both mouse and human development. The expression pattern of GATA-3 during embryonic development, at least at the tissue level, is highly conserved among different vertebrates. In immune cells, GATA-3 is best known to function as a master regulator of T-helper-2 (Th2) cell differentiation (Zhang DH, 1997). Additional crucial functions in early T cell commitment, b-selection, and CD4+ T cell development.

STUDY ON GATA-3 AND ITS ROLE

History

GATA-3 is one of the first genes that are transcriptionally activated in hematopoiesis as early as

hematopoietic stem cells (HSCs) stage (Debacker C *et al.*, 1998).

ROLE IN THYMOPOIESIS AND LYMPHOPOIESIS

- In early stages of thymopoiesis, GATA-3 has been shown to contribute to intermediate stages, especially the DN2-DN3-DN4 transition, of T cell development
- GATA-3 has been shown to contribute to intermediate stages, especially the DN2-DN3-DN4 transition, of T cell development.
- Definite information about the expression and role of GATA-3 in early stages of lymphopoiesis was provided by studies using various GATA-3 mutant mice.

ROLE OF GATA-3 AND NATURAL KILLER CELLS (NKT)

- 1) Potential role for GATA-3 in development, maturation, and function of invariant NKT (iNKT) cells. These cells are a unique subset of T cells expressing Va14Ja18 (mouse) or Va24Ja18 (human)
- 2) T cell receptors, which often dimerize with Vb8, Vb7, or Vb2. Similar to the conventional a/b T cells, iNKT cells also originate from thymic DP cells but they are positively selected by CD1d molecules.
- 3) Subsequent to successful positive selection, iNKT cells differentiate into either CD4+ or CD4-CD8- mature iNKT cells that constitute approximately 5% of the peripheral T cell pool (Kinjo Y *et al.*, 2005).

ROLE OF iNKT Cells

- 1) Unique T cell subset has been shown to rapidly produce large amounts of various Th1 and Th2 cytokines including IFN- γ , IL-4, and IL-13, a phenomenon called cytokine storm.
- 2) Multiple studies have demonstrated that iNKT cells play a crucial immunomodulatory role not only against infections, but are also involved in autoimmunity, allergy, and cancer.

STUDY OF GATA-3

Loss-of-function approach or by enforced expression of GATA-3

GATA 3 DELETED MICE

Mice in which GATA-3 was deleted using Cd4-Cre. GATA-3-deficient iNKT cells failed to respond to the NKT cell agonist α -galactosylceramide in vivo and mount a cytokine storm. This unresponsiveness is possibly due to defects in TCR signal transduction and was probably upstream of protein kinase C and calcium influx. This is because GATA-3-deficient iNKT cells were still capable of producing IFN- γ but not Th2 cytokines like IL-4, IL-5, or IL-13 that suggests that

GATA-3 has a similar role in iNKT cells as in conventional T cells (Naoe Y *et al.*, 2007).

ROLE OF GATA-3 IN Th2 DIFFERENTIATION History

Initial clue for the involvement of GATA-3 in Th2 differentiation was provided by a prior study by Ray and colleagues that identified GATA-3 binding to the IL-5 promoter that was crucial for cyclicAMP-induced expression of the cytokine gene in T cells (Siegel MD *et al.*, 1995)

GATA-3 as a key transcription factor that is essential for Th2 differentiation is without doubt the most studied function of this protein. The role of this transcription factor as a master regulator of Th2 differentiation was independently co-discovered in the laboratories of Ray and Flavell (Zhang DH *et al.*, 1988)

GATA -3 AND INTERLEUKIN (IL4 & IL5)

- 1) Th2 cells, antisense GATA-3 RNA inhibited IL-5 but not IL-4 promoter activation
- 2) Rao and colleagues showed that a distal enhancer in the IL-4 gene binds GATA-3 to induce its expression (Agarwal S *et al.*, 2000)
- 3) Expression of GATA-3 is significantly up regulated in human cells that express Th2 cytokine genes (Nakamura Y *et al.*, 1999)

AUTOACTIVATE OF GATA-3

History

PROPERTY OF AUTO ACTIVATION

GATA-3 was a serendipitous finding in the laboratory of Murphy when they were investigating the mechanism underlying the ability of GATA-3 to promote Th2 differentiation in a STAT6-independent fashion (Ouyang W *et al.*, 2000)

MAINTENANCE AND AMPLIFICATION OF THE Th 2

Efficiently promoted by auto activation of endogenous GATA-3 expression. p38 MAPK was shown to be important for cAMP-mediated phosphorylation of GATA-3 that promotes Th2 cytokine gene expression (Chen CH *et al.*, 2000).

NOTCH SIGNALING AND GATA-3

Notch signaling has been implicated in Th2 differentiation by directly regulating GATA-3 expression although more studies are needed to determine the importance of this regulation in vivo.

INTERPLAY OF GATA-3 AND OTHER TRANSCRIPTION FACTORS AND IL4

1) GATA 3 is a critical transcription factor for many developmental processes. During T helper (Th) cell

differentiation, GATA3 induces the Th2 and suppresses the Th1 pathway. Stimulation of the T cell receptor (TCR) of naive Th cells in the presence of interleukin 4 (IL-4) induces robust expression of GATA3; however, it is unclear where these signals integrate (Eyal J *et al.*, 2000).

2) GATA3 encodes two transcripts that differ in their alternative, un translated first exons.

The involvement of the TCR-inducible transcription factor NFAT1 in the transcriptional regulation of both Gata3 transcripts following TCR stimulation of naive and differentiated Th2 cells.

3) IL-4 is important for the initiation and establishment of GATA3 transcription in developing Th2 cells, especially from the distal promoter. The early function of IL-4 can be STAT6 dependent or independent. However, the establishment of the activity of the distal promoter is totally dependent on STAT6, whereas it is likely that the proximal promoter has additional activation mechanisms that are STAT6 independent. different combinations of transcription factors downstream of the IL-4 receptor (IL-4R) and TCR finely Modulate GATA3 gene expression from its two promoters for optimal Th2 differentiation.

ASTHMA AND Th2 CELLS

1) Asthma is a pathological condition associated with an overzealous Th2 response in response to innocuous antigens resulting in mucus production and eosinophilic infiltration.

2) Studies have documented that asthmatics have a higher percentage of CD4+ T cells producing IL-4, IL-5, and IL-13 which are secreted in the airways of patients with asthma.

3) GATA-3 mRNA expression is significantly increased in the airways of asthmatic subjects compared with that in normal control subjects and positively correlates with IL-5 expression.

4) Mice expressing a dominant negative mutant of GATA-3 demonstrate reduced inflammation, low IgE levels and blunted eosinophilia (Nakamura Y *et al.*, 1999; Robinson DS *et al.*, 1992; Walker C *et al.*, 1992; Zhang DH *et al.*, 1999).

CORTICOSTEROIDS INHIBIT GATA-3

Corticosteroids which are commonly used to treat allergic diseases, have a potent inhibitory effect on GATA-3 in T cells by competing for importin- α and by inducing the expression of a p38 MAPK inhibitor (Zhang DH *et al.*, 1999).

STUDIES SUPPORTING GATA-3 AS MOLECULAR TARGET

1) Delivering antisense GATA-3 reduced airway inflammation.

2) T-bet-deficient mice demonstrate spontaneous induction of asthma even in the absence of

Immunological challenge with enhanced eosinophilia and airway hyper-responsiveness (Finotto S *et al.*, 2001; Finotto S, *et al.*, 2002).

LATEST REPORT ON TRIAL DONE

Inactivation of GATA 3

SB010:- a novel DNA enzyme (DNA zyme) that is able to cleave and inactivate GATA3 messenger RNA (mRNA). Result of study show modified response in allergic patient.

The potential of such therapy in controlling asthma by immune modulation should be tested verified

by taking up further studies and targeting GATA 3 by antisense therapy or by pharmacological approach (Naoe Y *et al.*, 2007).

ACKNOWLEDGEMENT

None

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

- Agarwal S, *et al.* Cell-type-restricted binding of the transcription factor NFAT to a distal IL-4 enhancer *in vivo*. *Immunity*, 12(6), 2000, 643–645.
- Allergen A. Responses Modified by a GATA3 DNAzyme. *N Engl J Med*, 373, 2015, 1176-1177.
- Amsen D, *et al.* Direct regulation of Gata3 expression determines the T helper differentiation potential of Notch. *Immunity*, 27(1), 2007, 89–99.
- Anuradha R and Lauren C. Th2 cells and GATA-3 in asthma: new insights into the regulation of airway inflammation. *J Clin Invest*, 104(8), 1999, 985–993.
- Chen CH, *et al.* Cyclic AMP activates p38 mitogen-activated protein kinase in Th2 cells: phosphorylation of GATA-3 and stimulation of Th2 cytokine gene expression. *J Immunol*, 165(10), 2000, 5597–605.
- Debacker C, *et al.* Embryonic expression of the human GATA-3 gene. *Mech Dev*, 85(1–2), 1998, 183.
- expression of the T cell receptor alpha gene. *EMBO J*, 10(5), 1991, 1187–1192.
- Eyal Y, *et al.* Transcriptional Regulation of *Gata3* in T Helper Cells by the Integrated Activities of Transcription Factors Downstream of the Interleukin-4 Receptor and T Cell Receptor. *Development*, 23, 2004, 43.
- Finotto S, *et al.* Development of spontaneous airway changes consistent with human asthma in mice lacking T-bet. *Science*, 295(5553), 2002, 336–338.
- Finotto S, *et al.* Treatment of allergic airway inflammation and hyperresponsiveness by antisense-induced local blockade of GATA-3 expression. *J Exp Med*, 193(11), 2001, 1247–1260.
- George KM, *et al.* Embryonic expression and cloning of the murine GATA-3 gene. *Development*, 120(9), 1994, 2673–86.
- Ho IC, *et al.* Human GATA-3: a lineage-restricted transcription factor that regulates the
- Hosoya T, *et al.* From the cradle to the grave: activities of GATA-3 throughout T-cell development and differentiation. *Immunol Rev*, 238(1), 2010, 110–125.
- Kinjo Y, Kronenberg M. V alpha14 i NKT cells are innate lymphocytes that participate in the immune response to diverse microbes. *J Clin Immunol*, 25(6), 2005, 522–33.
- Maneechotesuwan K, *et al.* Suppression of GATA-3 nuclear import and phosphorylation: a novel mechanism of corticosteroid action in allergic disease. *PLoS Med*, 6(5), 2009, e1000076
- Maneechotesuwan K, *et al.* Suppression of GATA-3 nuclear import and phosphorylation: a novel mechanism of corticosteroid action in allergic disease. *PLoS Med*, 6(5), 2009, e1000076.
- Nakamura Y, *et al.* Gene expression of the GATA-3 transcription factor is increased in atopic asthma. *J Allergy Clin Immunol*, 103(2 Pt 1), 1999, 215–222.
- Naoe Y, Setoguchi R, Akiyama K, Muroi S, Kuroda M, Hatam F, Littman DR, Taniuchi I. Repression of interleukin-4 in T helper type 1 cells by Runx/Cbf β binding to the *Il4* silencer. *J Exp Med*, 204, 2007, 1749–55
- Ouyang W, *et al.* Stat6-independent GATA-3 autoactivation directs IL-4-independent Th2 development and commitment. *Immunity*, 12(1), 2000, 27–37.
- Robinson DS, *et al.* Predominant TH2-like bronchoalveolar T lymphocyte population in atopic asthma. *N Engl J Med*, 326(5), 1992, 298–30
- Siegel MD, *et al.* Activation of the interleukin-5 promoter by cAMP in murine EL-4 cells requires the GATA-3 and CLE0 elements. *J Biol Chem*, 270(41), 1995, 24548–55.
- Walker C, *et al.* Allergic and nonallergic asthmatics have distinct patterns of T-cell activation and cytokine production in peripheral blood and bronchoalveolar lavage. *Am Rev Respir Dis*, 146(1), 1992, 109–115.
- Yamamoto M, *et al.* Activity and tissue-specific expression of the transcription factor NF-E1 multigene family. *Genes Dev*, 4(10), 1990, 1650–1662.

- Zhang DH, *et al.* Differential responsiveness of the IL-5 and IL-4 genes to transcription factor GATA-3. *J Immunol*, 161(8), 1998, 3817–3821.
- Zhang DH, *et al.* Inhibition of allergic inflammation in a murine model of asthma by expression of a dominant-negative mutant of GATA-3. *Immunity*, 11(4), 1999, 473–82.
- Zhang DH, *et al.* Transcription factor GATA-3 is differentially expressed in murine Th1 and Th2 cells and controls Th2-specific expression of the interleukin-5 gene. *J Biol Chem*, 272(34), 1997, 21597–21603.