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Functions of Runx in IgA Class Switch Recombination

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ABSTRACT

Runt-related (*Runx*) transcriptional regulators play essential roles in various cell fate determination processes, and dysfunction of these regulators causes many human diseases. Considerable insight into the functions of Runx proteins was provided mainly by studies of hematopoietic and skeletal disorders. Recently, extensive investigations have revealed new functions of these transcription factors in immune cell differentiation and functioning. In the present review, we discuss the mechanisms of selective IgA production in the intestine and report the involvement of Runx proteins in this process. J. Cell. Biochem. 112: 409–414, 2011. © 2010 Wiley-Liss, Inc.

KEY WORDS: RUNX; IGA; CLASS SWITCH RECOMBINATION; GERMLINE TRANSCRIPTION; INTESTINE

Runt-related (*Runx*) genes are evolutionarily conserved transcription factors that determine cell fate by regulating lineage-specific gene expression. Three *Runx* genes have been reported in mammals; *Runx1* plays a key role in definitive hematopoiesis and is frequently involved in the pathogenesis of human leukemia [Okuda et al., 1996; Wang et al., 1996; Osato, 2004; Chen et al., 2009], *Runx2* is essential for bone development [Komori et al., 1997; Otto et al., 1997] and haploinsufficiency of it causes cleidcranial displasia, and *Runx3* is a tumor suppressor involved in gastric cancer [Li et al., 2002]. In addition, *Runx3* has more widespread regulatory roles in the differentiation and functioning of various cell types, including T cells [Taniuchi et al., 2002; Kohu et al., 2005; Sato et al., 2005], dendritic cells (DCs) [Fainaru et al., 2004], natural killer cells [Ohno et al., 2008], B cells [Watanabe et al., 2010], and proprioceptive dorsal root ganglion neurons [Inoue et al., 2002; Levanon et al., 2002].

Immunoglobulin A (IgA) is the most abundantly produced Ig in vivo. In contrast to IgG, which plays a key role in systemic immune reactions through secretion into the blood, IgA is predominantly secreted into the gastrointestinal tract. In addition to the protection against mucosal pathogenic microorganisms, neutralization of toxins, and protection from epithelial penetration of microorganisms, IgA controls the size and species of the bacterial flora in the intestine [Cerutti and Rescigno, 2008; Macpherson et al., 2008; Mora and von Andrian, 2009; Stavnezer and Kang, 2009; Fagarasan et al., 2010]. Among the various factors, TGF-β1 plays a special role in IgA class switch recombination (CSR) because TGF-β1 is required for IgA switch induction of splenic B cells in vitro [Sonoda et al., 1989]; it was also reported that TGF-β1-deficient and B cell-specific TGF-β1 receptor II-deficient mice have low levels of IgA [van Ginkel et al., 1999; Cazac and Roes, 2000]. Recent findings indicate that Runx proteins play essential roles in this signaling pathway [Shi and Stavnezer, 1998; Hanai et al., 1999; Pardali et al., 2000; Zhang and Derynck, 2000; Ito and Miyazono, 2003; Miyazono et al., 2004; Javed et al., 2008].

CSR REGULATION

Humoral immunity is dependent on the expression of antibodies that are specific for foreign antigens and that possess specialized effector functions. To generate diverse antigen receptors, variable (V), diversity (D), and joining (J) gene segments are assembled through a process known as VDJ recombination during early B cell development. After migration to secondary lymphoid organs, antigen-stimulated mature B cells replace their Cμ constant region gene with other constant region isotypes through CSR. Therefore, CSR is required for the expression of antibodies that have the same antigen specificity but a different effector function. This process is mediated by an intrachromosomal recombinational event between the switch (S) region of the Cμ region and one of the downstream S regions. The target specificities of CSR are determined by cytokines through the control of germ line transcription (GLT) [Honjo et al., 2002; Chaudhuri and Alt, 2004; Ramiro and Nussenzweig, 2004; Sugai et al., 2005; Longerich et al., 2006; Stavnezer et al., 2008]. For example, interferon-γ induces GLT of γ2a, whereas TGF-β1 induces GLT of γ2b and α. On the other hand, interleukin-4 induces GLT of γ1 and ε. GLT initiates CSR by

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recruiting activation-induced cytidine deaminase (AID) to target loci [Nambu et al., 2003]. Recent studies indicated that stalled RNA polymerase II and Stg5 are required for AID recruitment to target loci [Pavri et al., 2010]. After deamination of the deoxycytidine at the transcribed S regions by AID, double-strand breaks generated by base excision repair or mismatch repair machineries are repaired by the nonhomologous end joining pathway [Honjo et al., 2002; Chaudhuri and Alt, 2004; Ramiro and Nussenzweig, 2004; Sugai et al., 2005; Longerich et al., 2006; Stavnezer et al., 2008] (Fig. 1).

SITES AND FACTORS FOR GENERATION OF IgA-PRODUCING CELLS

In germ-free mice, IgA production in the intestinal mucosa is severely affected; however, the IgA production normalizes within a few weeks following intestinal bacterial colonization. Thus, IgA production depends on bacterial stimulation in the intestine [Hooper and Macpherson, 2010]. Accordingly, skewed IgA CSR occurs in gut-associated lymphoid tissues (GALTs) called Peyer's patches, isolated lymphoid follicles, and the lamina propria (LP) of the intestine [Cerutti and Rescigno, 2008; Macpherson et al., 2008; Stavnezer and Kang, 2009; Fagarasan et al., 2010; Hooper and Macpherson, 2010]. However, the serum IgA level in germfree mice is maintained at approximately half the level maintained in normal mice, suggesting that serum IgA is partly produced in a manner independent of mucosal IgA.

In general, CSR requires two signals; one stimulates GLT of specific isotypes induced by several cytokines, and another is delivered by ligation of CD40 on B cells with the CD40 ligand (CD40L) on activated T cells. However, IgA production is not so abrogated in CD40- or CD40L-deficient mice and humans,

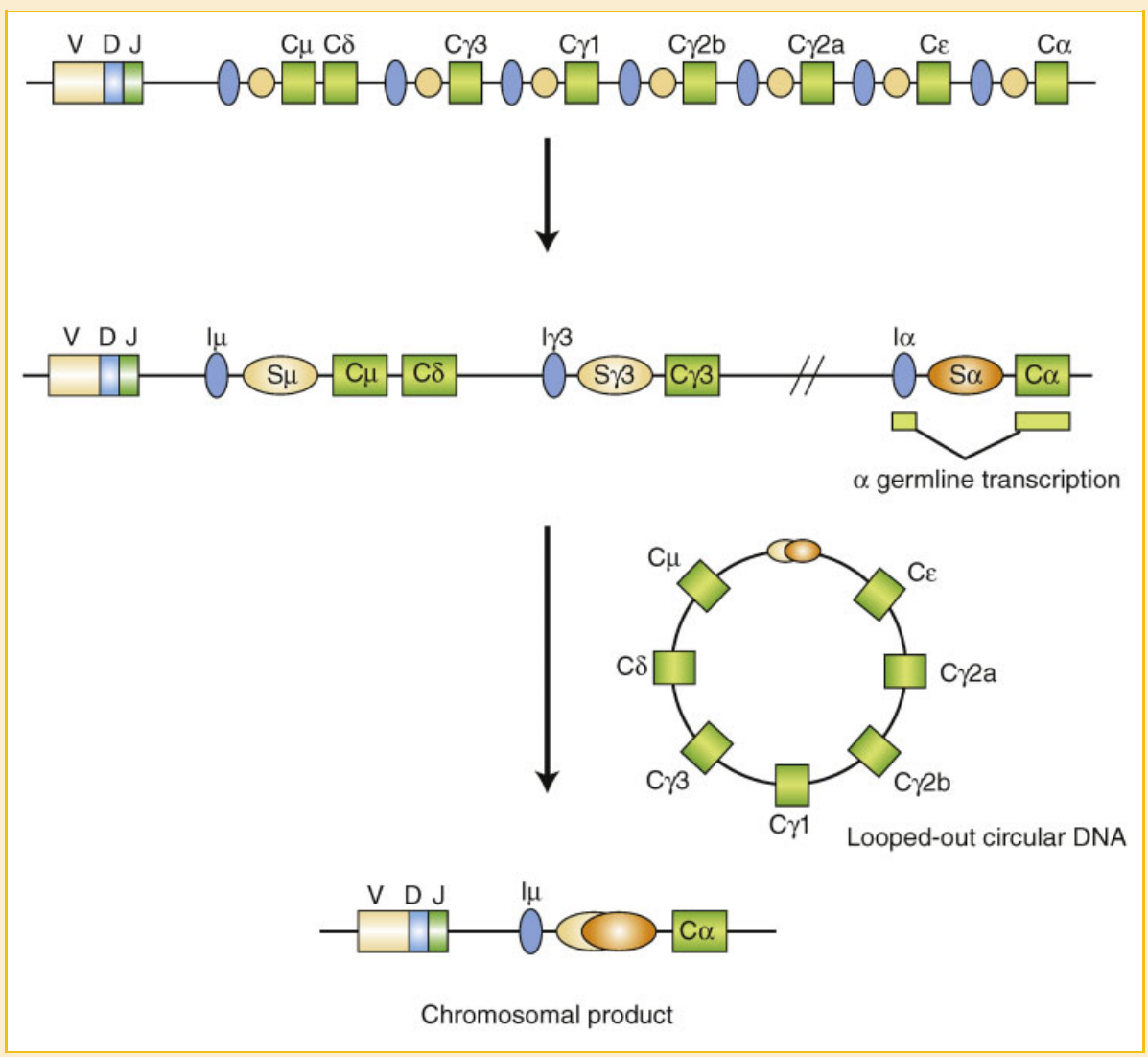

Fig. 1. Schematic representation of the murine heavy chain locus. The variable region of the immunoglobulin heavy chain gene is assembled from VH, DH, and JH gene segments by VDJ recombination. After completing VDJ recombination at heavy and light chain loci, B cells produce IgM antibody. Subsequently, secondary isotypes are produced by CSR, which exchanges the Cμ constant region gene for other downstream constant region genes. The CSR target is determined by cytokines through the induction of GLT at the target locus. For IgA CSR, TGF-β1 and RAs induce αGLT and promote IgA CSR.

indicating the existence of other costimulatory signals for IgA CSR. As expected, B cell-activating factor of tumor necrosis factor family (BAFF, also known as BLyS) and a proliferation-inducing ligand (APRIL) were identified as structurally and functionally related to CD40L and were found to stimulate CSR to IgG and IgA in vitro. B cells express three receptors for these cytokines, BAFF receptor (BAFF-R), transmembrane activator, and CAML interactor (TACI), and B cell maturation antigen (BCMA). BAFF interacts with all three receptors, whereas APRIL binds BCMA and TACI. Because BAFF- or BAFF-R-deficient mice display defects in B cell generation, IgA CSR cannot be estimated in these models. TACI mutations have been found in IgA-deficient and common variable immunodeficient individuals. In addition, TACI-deficient mice show low IgA levels [von Bulow et al., 2001]. One line of APRIL-deficient mice displayed IgA deficiency [Castigli et al., 2004], while another line that generated independently showed normal IgA levels [Varfolomeev et al., 2004]. The biological relevance of BAFF and APRIL signaling in IgA CSR was thus estimated. Recently, it was reported that a DC subset from small intestinal LP and GALT produces BAFF and APRIL via Toll-like receptor (TLR) signaling [Tezuka et al., 2007] (Fig. 2), the family of which comprises various pattern recognition receptor families that are required for sensing microorganisms by recognizing several molecules expressed by these microorganisms. In addition, it was demonstrated that human colon epithelial cells express BAFF and APRIL during

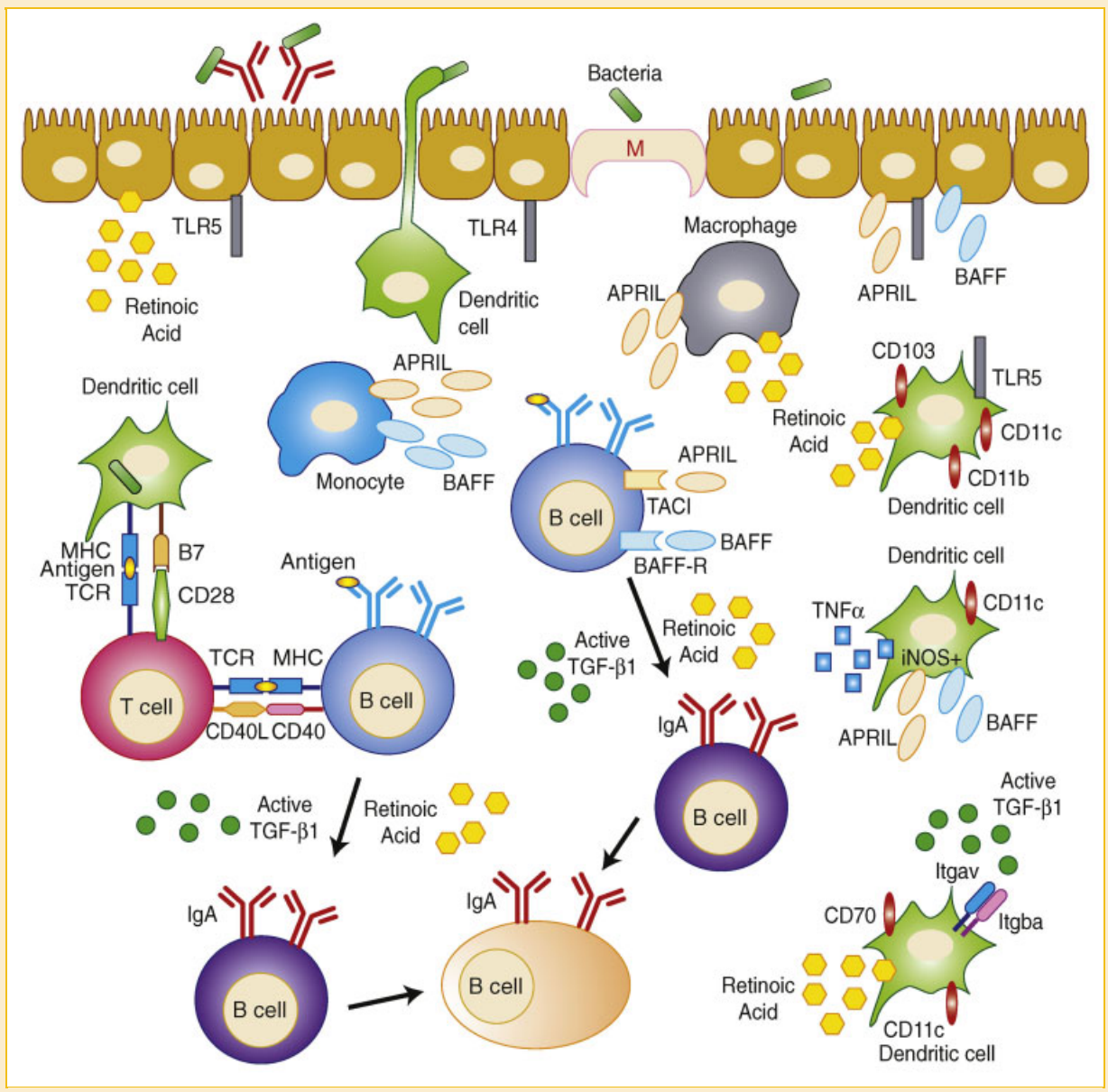

Fig. 2. IgA production in the intestine. IgA CSR requires T cell help (CD40L) or BAFF/APRIL signaling. In addition to these signals, all-trans retinoic acids and TGF-β1 are required for inducing αGLT. In the intestine, epithelial cells, DCs, macrophages, and monocytes produce APRIL and BAFF. In addition, many cell types produce RA as shown here. Recent studies indicated that there are various DC subsets within the intestine; known surface markers and their cytokine-producing properties are also shown.

stimulation with TLR (Fig. 2). These activities are believed to contribute to local switching to IgA in the colon.

The involvement of retinoic acids (RAs) in IgA production was demonstrated previously using vitamin A-deficient mice and rats. In vitamin A-deficient mice, reduced numbers of IgA-producing cells were observed in LP of the small intestine; the level of IgA in the serum, however, was not affected [Mora et al., 2006]. Thus, the effect of RA on IgA production is not systemic but is specific to the intestine. Recent studies further indicated that DCs from GALT or LP, but not from the spleen, have the ability to enhance IgA CSR partly by producing RA via the oxidation of RA precursors [Mora et al., 2006; Uematsu et al., 2008] (Fig. 2). Several reports further noted that intestinal epithelial cells and intestinal LP macrophages also express retinal dehydrogenases and secrete RA (Fig. 2). Analysis of mice deficient in the inducible form of nitric oxide synthase (iNOS) showed that IgA CSR in vivo is dependent on this enzyme. iNOS is expressed by DCs from LP and GALT but not from the spleen, and this expression of iNOS depends on TLR signaling (Fig. 2). NO produced by iNOS appears to be important for the normal expression of TGF-β1 receptor II, Smad3, and Runx3 in activated B cells, as well as for the production of BAFF and APRIL by DCs [Tezuka et al., 2007].

It is also well known that GALT and LP are rich in TGF-β1. In addition, subsets of LPDCs and LP stromal cells (LSCs) promote IgA CSR partly through TGF-β1 secretion. Moreover, mucosal DCs express the integrins αvβ6 and αvβ8, which activate latent TGF-β1 in vivo [Atarashi et al., 2008] (Fig. 2). These findings further support the hypothesis that GALTs are rich in IgA-inducing factors, and thus skewed IgA CSR takes place in the intestine. In summary, various intestinal cells have sensing systems for bacterial invasion, one of which is TLR, and these cells utilize the sensing signals to create optimal conditions for IgA CSR promotion.

RUNX FUNCTIONS IN IgA PRODUCTION

As described above, various types of cells in the intestinal region contribute to the establishment of optimal conditions for skewed IgA CSR. Because Runx proteins are expressed in intestinal epithelial cells, DCs, macrophages, T cells, and B cells, the functions of Runx may include the regulation of IgA production in vivo [Mora and von Andrian, 2009]. Among the three Runx proteins, special attention has been paid to Runx3, as loss of this protein is associated with defects in DC function and development of colitis and asthma-like features [Brenner et al., 2004; Fainaru et al., 2004]. Runx3-deficient mice have a defect in DC function in response to TGF-β1, which is not believed to be directly related to its function in IgA production. On the other hand, accumulating evidence indicates that Runx3 is a positive regulator for CD103 expression in various cell types [Grueter et al., 2005]. Furthermore, it was shown that mucosal CD103+ DCs can induce regulatory T cells via TGF-β1 and RA-dependent mechanisms [Coombes et al., 2007]; both these factors are also required for IgA CSR (Fig. 2). Accordingly, it is believed that Runx3 should work as a positive regulator for IgA CSR acting within DCs. However, to elucidate its role, further and more extensive investigations are required.

Several studies revealed that Runx transcription factors act in concert with Smad proteins in their response to the signals of the TGF-βfamily. Runx and Smad proteins interact with each other and can enhance transcription synergistically, as demonstrated in reporter assays using the promoter of αGLT [Shi and Stavnezer, 1998; Hanai et al., 1999; Pardali et al., 2000; Zhang and Derynck, 2000; Javed et al., 2008]. Expression analysis of various Runx proteins in I.29, CH12, and splenic B cells under IgA-inducing conditions suggests that Runx3 is responsible for IgA CSR [Shi and Stavnezer, 1998]. Therefore, Runx3 is believed to function as an activator of IgA CSR in B cells. In this regard, Groner et al. demonstrated that Runx3-deficient B cells exhibited impaired IgA CSR in vitro, whereas the IgA levels in bronchoalveolar lavage from Runx3-dificient mice were increased significantly. Such discrepancies can be attributed partly to the difficulty in investigating IgA CSR in vitro. At the time of the study by Groner et al., the efficiency of the in vitro IgA CSR system was extremely low. In our recent study, we examined the effect of Runx3-deficiency in IgA CSR in a different genetic background using the same experimental setting and confirmed the results from Groner's study; we found that Runx3 exhibits some positive role in IgA CSR. However, defects in IgA CSR of Runx3-deficient B cells cannot be observed always, which indicates that various unknown factors may affect the results. Because all three Runx proteins are expressed in B cells and Runx1 is required for hematopoietic stem cell generation, we examined the effects of Runx2 and Runx3 on IgA CSR. Furthermore, Runx2- and Runx3-deficient mice died within a short period after birth; therefore, we generated Runx2/3-deficient lymphocytes in RAG2$^{-/-}$ mice by infusing Runx2/3-deficient fetal liver cells. As expected, IgA production was almost completely blocked in the RAG2$^{-/-}$ mice having Runx2/3-deficient lymphocytes [Watanabe et al., 2010].

To determine the Runx protein signals involved in IgA CSR, we established an efficient IgA CSR system using only soluble factors and found that RA and TGF-β1 act in synergy to induce IgA CSR. In this in vitro IgA switching system, APRIL played a special role. The addition of APRIL, but not BAFF, to the culture system enhanced the efficiency of IgA CSR significantly. We further determined the effect of APRIL on αGLT and found that the enhancement was not significant. Moreover, APRIL may have promoted cell survival in this specialized culture system. Therefore, we propose that APRIL and BAFF function as B cell survival factors in various IgA switch-inducing conditions in vivo, in addition to their known functions in inducing αGLT. Using this system, we found that Runx proteins are required not only for TGF-β1-dependent IgA CSR but also for RA-dependent IgA CSR. The existence of both pathways in IgA CSR is supported by observations where serum IgA levels in RAG2$^{-/-}$ mice with Runx2/3-deficient lymphocytes were found to be lower than the serum IgA levels in TGF-β1-deficient mice.

In Runx2/3-deficient B cells, IgA CSR by TGF-β1 is completely blocked. This indicates that TGF-β1-Smad signaling pathways work only in the presence of Runx proteins at the αGL promoter. In addition, Runx binding to Smad proteins and TAZ are not required for induction of αGLT and consequent IgA CSR. Therefore, Runx proteins function as synergistic coregulators of αGLT or provide accessible chromatin structures to Smad proteins, independent of their interaction.

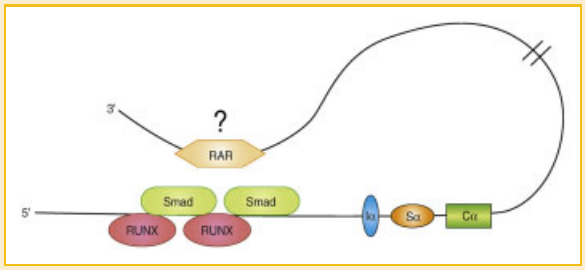

Fig. 3. Regulation of α germline promoter αGL promoter contains Runx and Smad binding sites but not RARE.

The involvement of Runx proteins in RA-dependent IgA CSR was confirmed using Runx2/3-deficient B cells. However, we could not determine the exact retinoic acid receptor response element (RARE) within the αGL promoter. Elucidating the mechanism of action of RAR and Runx proteins in the induction of αGLT is the next important issue. Currently, we are investigating the genuine RARE within the 3' enhancer of the heavy chain locus as well as examining the physical interaction between Runx and RAR proteins (Fig. 3).

In conclusion, we report that Runx proteins play pivotal roles in establishing good relationships between various commensal bacteria and provide a healthy intestinal environment by regulating the action of various cell types, including epithelial cells, DCs, T cells, and B cells in the intestine. Increased knowledge of the functions of Runx proteins in these cell types will facilitate the understanding of how Runx proteins work in general. This information is expected to contribute to understanding the functions of Runx proteins in tumorigenesis, cell differentiation, and other important biological issues.

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