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Review

# The role of inhibitor of binding or differentiation 2 in the development and differentiation of immune cells

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ABSTRACT

Inhibitor of binding or differentiation 2 (Id2), a member of helix-loop-helix (HLH) transcriptional factors, is recently reported as an important regulator of the development or differentiation of immune cells. It has been demonstrated that Id2 plays a critical role in the early lymphopoiesis. However, it has been discovered recently that Id2 displays new functions in different immune cells. In the adaptive immune cells, Id2 is required for determining T-cell subsets and B cells. In addition, Id2 is also involved in the development of innate immune cells, including dendritic cells (DCs), natural killer (NK) cells, and other innate lymphoid cells (ILCs). Here, we review the current reports about the role of Id2 in the development or differentiation of main immune cells.

## 1. Introduction

The inhibitor of DNA binding or differentiation (Id) is a member of helix-loop-helix (HLH) proteins, which belong to E protein family. In mammals, the Id family has four members (Id1–Id4). In 1990, Benezra et al discovered and identified the first Id protein which was named as Id1 (Benezra et al., 1990). Then, Id2 and Id3 were identified or cloned in 1991 (Sun et al., 1991), (Christy et al., 1991). Id4 was found by Riechmann et al., 1994, 1994). Like other members of HLH protein family, Id protein has a highly conserved domain named HLH (Benezra et al., 1990). The conserved regions are consisting of three components: two amphipathic α helices called "helix" with 15 ~ 20 residues and a shorter peptide named "loop". Nearly all members of HLH proteins have a basic region with 10 ~ 20 amino acid, which locates in the N-terminal of helix 1 (Fig. 1). Through this domain, bHLH proteins can be guided to bind to DNA containing E boxes (CANNTG), N boxes (CACNAG) or Ets sites (GGAA/T) to promote or repress the transcription (Zebedee and Hara, 2001). The HLH domain has a significant role in regulating gene expression by forming homo-dimerization or hetero-dimerization when recognizing their targets (Ellenberger et al., 1994).

Whereas, Id proteins lack this basic region (Benezra et al., 1990) (Fig. 1). It results in that they cannot bind to DNA containing E/N boxes to regulate associated genes. But Id proteins can form a complex with bHLH proteins to arrest them binding to DNA. Therefore, Id proteins can be regarded as inhibitors of bHLH. Since the main function of bHLH is promoting the differentiation of cells, Id proteins perform as inhibitors of cell differentiation and DNA binding (Benezra et al., 1990), (Joan Garrell, 1990), (Ellis et al., 1990) and promoters of cell proliferation (Iavarone et al., 1994).

However, different Id protein also has different functions in immune system. In different Id-null mouse models, scientists disclosed that the deletion of Id1 influenced the T-cell migration (Sikder et al., 2003). $Id2^{-/-}$ mice lack lymph nodes and Peyer's patches and the number of natural killer cells(Yokota et al., 1999), Langerhan's cells and splenic dendritic cells decreased (Hacker et al., 2003), (Kusunoki et al., 2003). Id3-delection impact on the humoral immunity and B-cell proliferation. Unlike other Id proteins, Id4 mainly functions in neural proliferation. Among these four members, Id2 performs more roles than other

*Abbreviations:* Id, inhibitor of DNA binding or differentiation; HLH, helix-loop-helix; HSC, hematopoietic stem cell; CLP, common lymphoid precursor; Treg, regulatory T; Th, helper T; Tfh, follicular helper T; NKT, natural killer T; MOG, myelin oligodendrocyte glycoprotein; MSC, mesenchymal stem cell; Gfi-1, growth factor independence 1; Ebf1, early B cell factor; CSR, class switch recombination; AID, activation-induced cytidine deaminase; MZ, marginal zone; HC, hodgkin lymphoma cell; DC, dendritic cells; MDC, myeloid dendritic cell; CMP, common myeloid progenitor cell; LDC, lymphoid dendritic cell; cDC, conventional dendritic cell; pDC, plasmacytoid dendritic cell; ILC, innate lymphoid cells; IFN-γ, interferon-γ; LTi, lymphoid tissue inducer; ILCP, innate lymphoid cell progenitor; FT, fetal thymus

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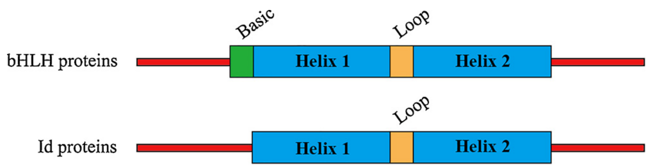


**Fig. 1.** Schematic structure of bHLH proteins and Id proteins.

members in immune cells. Thus, we highlight its role in the development and differentiation of several main immune cells in this review.

## 2. T cell

The progenitors of lymphocytes develop from the hematopoietic stem cells (HSCs) and differentiate into the common lymphoid precursors (CLPs). After that, a part of CLPs leaves the bone marrow and migrates into thymus as immature T lymphocytes (thymocytes) in which they develop into mature T cells. When arriving in the thymus, most T-cell precursors develop into αβ T cells, and the remaining become γδ T cells. In the next process of αβ T cell differentiation, these cells undergo three stages: double negative stage, double positive stage and single positive stage. After the negative and positive selections, the mature $CD4^+$ or $CD8^+$ naïve T cells are driven into peripheral immune organs or peripheral blood where the naïve T cells can further develop into other sub-populations. For example, after induced by different cytokines, $CD4^+$ naïve T cells can differentiate into regulatory T (Treg) cells (TGF-β) and different subsets of helper T (Th) cells, such as Th1 (IL-12), Th2 (IL-4), Th17 (IL-6/ TGF-β). In recent years, it is declared that Th2 cells can develop into a new subset T cell, follicular helper T (Tfh) cells, through interaction with B cells in the lymphoid follicle. Meanwhile, the $CD8^+$ naïve T cells can become cytotoxic T cells after stimulated with antigens. In addition to these subgroups mentioned above, T cells also have other lineages, such as natural killer T cells (NKT).

Most recent studies have shown that Id2 is a crucial transcription factor in the differentiation of Th cells. In the T cell-specific Id2-deficient mice, Lin et al disclosed that the population size of MOG (myelin oligodendrocyte glycoprotein) specific $CD4^+$ T cells is reduced and the interleukin-$17A^+$ (IL-$17A^+$) IFN-$\gamma^+$ $CD4^+$ T cells almost completely disappeared. It means that Id2 is required for the maintenance of these $CD4^+$T cells (Lin et al., 2012). Meanwhile, deletion of Id2 can influence the balance between Th1 and Tfh cells. Id2 may reinforce Th1 differentiation, but repress Tfh differentiation through regulating Th1-associated genes (*Slamf1, Cxcr6* and *Gzmb*) and Tfh-associated genes (*Cxcr5, Tcf7* and *Il6ra*), respectively (Shaw et al., 2016). E proteins, targets of Id2, play powerful roles in regulating Tfh differentiation. The E-Id protein axis can repress Tfh development by activating the PI3K-AKT-mTORC1 and c-myc/p19Arf pathway (Miyazaki et al., 2015). In the same way, at the early differentiation stage of Tfh cells, Bcl6, a transcriptional inhibitor, suppresses Id2 expression directly and allows E proteins promote CXCR5 expression to drive Tfh differentiation. However, E proteins upregulate the expression of Bcl6 via increasing the expression of Tef7 and Lef1. So E proteins and Bcl6 compose a positive feedback loop to promote Tfh differentiation in the Id2-delection mice (Shaw et al., 2016).

Moreover, Id2 also can also regulate the differentiation of $CD8^+$ T cells. Although the deletion of Id2 does not influence the proliferation and differentiation of $CD8^+$ naïve T cells during infection, it increases the apoptosis of effector cells by inhibiting associated genes (*Bcl2, Ctla4* and *Bcl2l11*) regulated by E proteins. Collectively, the repression of Id2 can result in the increase of IL-10 produced by $CD8^+$ T cells (Masson et al., 2014). Recently, it is found that sustained Id2 regulation of E proteins is required for effector $CD8^+$ T cells (Omilusik et al., 2018). It can inhibit the formation of $CD8^+$ memory cells via blocking E2A protein which binds to several key memory differentiation associated genes like *Tcf7* (Masson et al., 2013). Conditional deletion of Id2 may transform $KLRG1^{hi}$ "terminal" effector/effector-memory $CD8^+$ T cell population into a $KLRG1^{lo}$ memory-like population (Omilusik et al., 2018).

Furthermore, it is reported that the absence of Id2 resulted in a severe defect in the accumulation of hepatic invariant NKTs (iNKTs) in 1990 (Monticelli et al., 2009). Both Id2 and Id3 promoted iNKT cell lineage specification which results in innate-like tumor (D'Cruz et al., 2014), (Li et al., 2017).But both Mihalis et al and Louise et al demonstrated that Id2 could collaborate with Id3 to suppress thymic iNKTs (D'Cruz et al., 2014), (Verykokakis et al., 2013). Id2 was expressed in T-$BET^+$NKT1 cells, but Id3 was expressed in $PLZF^{high}$ NKT2 cells (D'Cruz et al., 2014). Meanwhile, Id2 involves in the process of the maintaining and homing of Treg with the present of Id3 (Miyazaki et al., 2014).

## 3. B cell

Bone marrow is the central immune organ where B cells originate and differentiate. HSCs differentiate into CLPs through recognizing FLT3 ligand expressed on the surface of mesenchymal stem cells (MSCs), then into pro-B cells. Furthermore, IL-7, secreted by matrix cells, leads B-cell progenitors following next developmental processes: B-cell precursors, immature B cells and mature B cells. Each stage is marked by various gene expression patterns and immunoglobulin (H and L chain) gene loci arrangement, the latter due to B cells undergoing V(D)J recombination as they development (Pelanda and Torres, 2012). At last, immature B cells migrate from bone marrow to the spleen as transitional B cells: T1 and T2 (Loder et al., 1999). When immature B cells migrate to the spleen, they are considered T1 B cells. In the spleen, T1 B cells become T2 B cells. T2 B cells differentiate into follicular B cells or marginal B cells. These cells can be considered mature B cells (Chung et al., 2003).

It has been demonstrated that B cell development is mediated by a transcriptional network comprised by transcriptional factors, such as Pax5, PU.1, Ikaros, EBF, E2A, Id2 and so on. PU.1 and Pax5 can be repressed by Id2 (Gonda et al., 2003),(Matthias and Rolink, 2005). It negatively regulates B cell differentiation and development (Ji et al., 2008), (Pongubala et al., 2008), (Becker-Herman et al., 2002), (Gore et al., 2010). Growth factor independence 1 (Gfi-1) can influences proliferation and differentiation of hematopoietic cells. Li and his colleagues disclosed that Gfi-1 could restrict B-cell progenitor development by inhibiting Id2, directly (Li et al., 2010). Jensen et al demonstrated that increased expression of Id2 repressed the efficient recombination of V(D)J and the differentiation of pre-B cells (Jensen et al., 2013), which might account for why the pre-B cell pool shrank with the age in human and mice (Rossi et al., 2003), (Jensen et al., 2010), (Johnson et al., 2002), (Cancro, 2005). The early B cell factor (Ebf1) can restore B cell differentiation in the IL-$7R\alpha^{-/-}$ mice through repression of E2A protein by Id2 (Thal et al., 2009). In Id2-deficient B cells, Sugai et al found that the switching recombination of IgE is increased (Sugai et al., 2003), because Id2 functions as a repressor of IgE class switch recombination (CSR) by inhibiting the activation of E2A and Pax5 which can bind to activation-induced cytidine deaminase (AID) (Gonda et al., 2003), (Sugai et al., 2004). Mad3, an antagonist of the c-Myc proto-oncogene product, can directly bind to the promoter of Id2 to suppress the B-cell differentiation in immature B cells and is opposite to Mad4 (Gore et al., 2010). Mercer et al also found that the Id2-HPC, a cell line with the multipotency both *in vitro* and *in vivo*, could differentiate into B cell through the repression of E2A by Id2 (Mercer et al., 2011). It was reported by Zhang et al that Notch signal could up-regulate the differentiation of marginal zone (MZ) B cells and down-regulate that of follicular (Fo) B cells by promoting the transcription of Id2 and Asb2 genes to regulate the expression of E2A (Zhang et al., 2013). Interestingly, Mathas et al demonstrated that the increased Id2 and ABF-1 could promote the lost or abnormal expression of B-cell specific genes which may result in Hodgkin lymphoma cells

(HC) derived from mature B cells (Mathas et al., 2006).

Above all, we can summary that although many transcription factors play important roles in the differentiation of B cells and most of them have some interaction with Id2. It is the reason of that many specific B-cell genes have E boxes in their promoters which can be recognized by E proteins (Kee et al., 2000). So these factors can regulate the B-cell maturation by Id2 to further influence the B-cell associated genes, especially E2A.

## 4. Dendritic cell

Dendritic cells (DCs), all originating from CD34$^+$ HSCs, are professional antigen presenting cells. DCs are normally divided into two categories: one, called myeloid dendritic cells (MDCs), is from common myeloid progenitor cells (CMPs); another, called lymphoid dendritic cells (LDCs), is from CLPs. Recently, scientists prefer to name MDCs as conventional dendritic cells (cDCs), and to name LDCs as plasmacytoid dendritic cells (pDCs). The two progenitors of cDCs, CD14$^+$CD11c$^+$CD1$^-$ monocytes and CD14$^+$CD11c$^+$CD1$^+$ monocytes, develop into mature DCs after undergoing four stages: progenitor phase, immature phase, migratory phase and mature phase. However, pDCs can develop from three origins: HSCs, peripheral blood and thymus. Both CLPs and CMPs can develop into Flt3$^+$ progenitors, and further differentiate into Langerhans cells (LCs, locating in the skin and intestinal epithelium), interstitial DCs (locating in heart, lungs, livers and kidney), and pDCs. Various transcriptional factors play important roles in the development of DCs, like Ikaros, Rel B, IRF-2, IRF-4, IRF-8, PU.1 and E2-2. Similarly, Id2 is also important for the differentiation of dendritic cells.

A growing body of evidence has implicated Id2 as playing a critical role in regulating the fate of DCs. It has been established that IRF8 can directly drive the progenitors into classic CD8α$^+$ DCs by targeting Id2 and Batf3 (Jaiswal et al., 2013), (Jackson et al., 2011). In Id2$^{-/-}$ mice, it is shown that the percentage of splenic CD8α$^+$ DCs is reduced (Hacker et al., 2003), (Kusunoki et al., 2003). However, another report has demonstrated that Id2 is not essential for the development of CD8α$^+$ DCs (Seillet et al., 2013). Thus, the detailed role of Id2 in CD8α$^+$ DCs is still under investigation.

Ets transcription factor Spi-B and E2-2 can promote pDC differentiation with the reduction of Id2. However, Spi-B cannot reverse the Id2 block in pDC development (Nagasawa et al., 2008). Zinc-finger transcription factor Bcl11 A which can regulate E2-2, Id2 and Mtg16, is required for pDC differentiation (Ippolito et al., 2014). Meanwhile, Ghosh et al proved that Mtg16, a member of ETO protein family, could promote pDC development and inhibit cDC differentiation by down-regulating Id2 expression (Ghosh et al., 2014). Zeb2, another Zinc-finger transcription factor, can facilitate pDCs and pre-cDCs to (XCR1$^-$SIRPα$^+$) cDC2 lineage by repressing Id2 directly (Scott et al., 2016). This result is just identical with what Spits et al found in 2000. They demonstrated that Id2 could inhibit the development of CD34$^+$CD38$^-$ progenitor cells into pre-DC2s but not into pre-DC1s (Spits et al., 2000). Opposite to CD8α$^+$ DCs, the HIF-1-induced Id2 represses induced pDCs with Flt3-L under hypoxia (Weigert et al., 2012). Interestingly, Schlitzer et al explored that CCR9- murine pDCs could be induced into cDC-like cells through down-regulating E2-2 and up-regulating Id2, PU.1 and Batf3. It means that Id2 can promote the differentiation of cDCs and repress the development of pDCs(Schlitzer A et al., 2011).

It is also established that Stat3 stimulates the expression of E2-2 which controls the population of pDCs, but Stat5 promotes the expression of Id2 to restrain CD103$^+$ DC differentiation (Li et al., 2012). Id2, Flt3-L and Irf8 can all regulate the nonlymphoid tissue CD103$^+$ DCs, same as lymphoid tissue CD8$^+$ DCs that come from the same progenitor (Hashimoto et al., 2011). Deletion of both Id2 and Irf8 or absence of Flt3-L makes HSCs fail to differentiate into CD103$^+$ DCs (Ippolito et al., 2014), (Ginhoux et al., 2009). Meanwhile, Id2 gene expression in CD103$^+$ DCs is higher than other DC subsets (Khandelwal et al., 2013).

Hacker et al discovered that Id2$^{-/-}$ mice lacked Langerhans cells (LCs). They believed in that Id2 could be reduced by the absence of TGF-β1 in LC development (Hacker et al., 2003). Similarly, Heinz et al demonstrated that TGF-β1 could up-regulate PU.1 and Id2 to promote CD34$^+$ HSCs into LCs (Heinz et al., 2006). Interestingly, Sere et al found two different types of LCs, long-term and short-term LCs. They demonstrated that Id2 was required for long-term LC development. Oppositely, the short-term LCs could develop from Gr-1$^{hi}$ monocytes with an Id2-indepentent condition (Sere et al., 2012). Meanwhile, Chopin et al disclosed that though Id2 and PU.1 were important to LC differentiation, the former was not necessary for the bone marrow derived LCs (Chopin et al., 2013).

To sum up, it is shown that Id2 is critical to DC differentiation. Although various proteins can interact with Id2 to influence DC development, the effect of Id2 acting on different subtypes of DCs are still unclear and how it functions is unknown.

## 5. Innate lymphoid cell

Innate lymphoid cells (ILCs) are a recently recognized group of lymphocytes which have the ability to resist the pathogens through secreting cytokines. But they lack the rearranged antigen-specific receptors. Based on the expression of lineage-specific transcription factors and discrete cytokine profiles, the identified ILCs can be divided into three subsets: ILC1s, ILC2s and ILC3s. ILC1s can produce the type1 cytokine interferon-γ (IFNγ), like natural killer (NK) cells (Bernink et al., 2013), (Diefenbach et al., 2014), (Fuchs et al., 2013). ILC2s which are GATA3 (Klein Wolterink et al., 2013) and RORα (Wong et al., 2012)dependent, produce IL-4, IL-5 and/or IL-13. ILC3s, like Th17 cells, produce IL17 and/or IL-22, such as lymphoid tissue inducer (LTi) cells (Diefenbach et al., 2014), (McKenzie et al., 2014). Different cytokines and transcriptional factors can guide innate lymphoid cell progenitors (ILCPs) differentiating into different ILCs. Among these cytokine and factors, Id2 plays a critical role in the development of ILCs.

The first report demonstrating the importance of Id2 in ILCs is based on the Id2-deficient mice. Yokota et al found that Id2$^{-/-}$ mice lack lymph nodes and Peyer's patches. Furthermore, the deletion of Id2 resulted in the reduction of NK cells which belonged to ILC1s (Yokota et al., 1999). The subsequent discovery also found that NK cells were reduced in Id2$^{-/-}$ fetal thymus (FT). The Id2$^{-/-}$ FT progenitors could not differentiate into NK cells in IL2-supplemented-fetal thymus organ culture (FTOC) (Ikawa et al., 2001). Other transcriptional factors, like E4bp4 (known as Nfil3), even long non-coding RNA (Mowel et al., 2017), can regulate IL-15 receptor to promote the progenitors into NK cells through Id2 (Schotte R et al., 2010), (Gascoyne et al., 2009), (Delconte et al., 2016), (Male et al., 2014). However, there are another points illustrating that Id2 does not influence NK cell progenitors, but regulates NK cell maturation (Nandakumar et al., 2013), (Boos et al., 2007).

Likewise, both ILC2s and ILC3s are reduced in Id2$^{-/-}$ mice (Moro et al., 2010), (Satoh-Takayama et al., 2010). Xu et al found that both adult and fetal ILC subsets were reduced in Nfil3$^{-/-}$ mice. They demonstrated that Nfil3 could regulate the expression of Id2 to influence ILCPs (Xu et al., 2015). Id2 also can maintain the balance of ILC3s and keep the production of IL-22 to resist the early attack of pathogens (Guo et al., 2015). In addition to promote T cell development, the activation of Notch signaling can repress ILC development through decreasing Id2 expression (Chea et al., 2016). Recently, it is also found that Id2 governs human ILC development from thymic progenitor cells toward immature CD5$^+$ ILCs (Nagasawa et al., 2017). Taken together, Id2 appears to drive ILC development by suppressing intrinsic B- and T-cell lineage potentials to allow for the expression of ILC-specific factors (Lim, 2015).

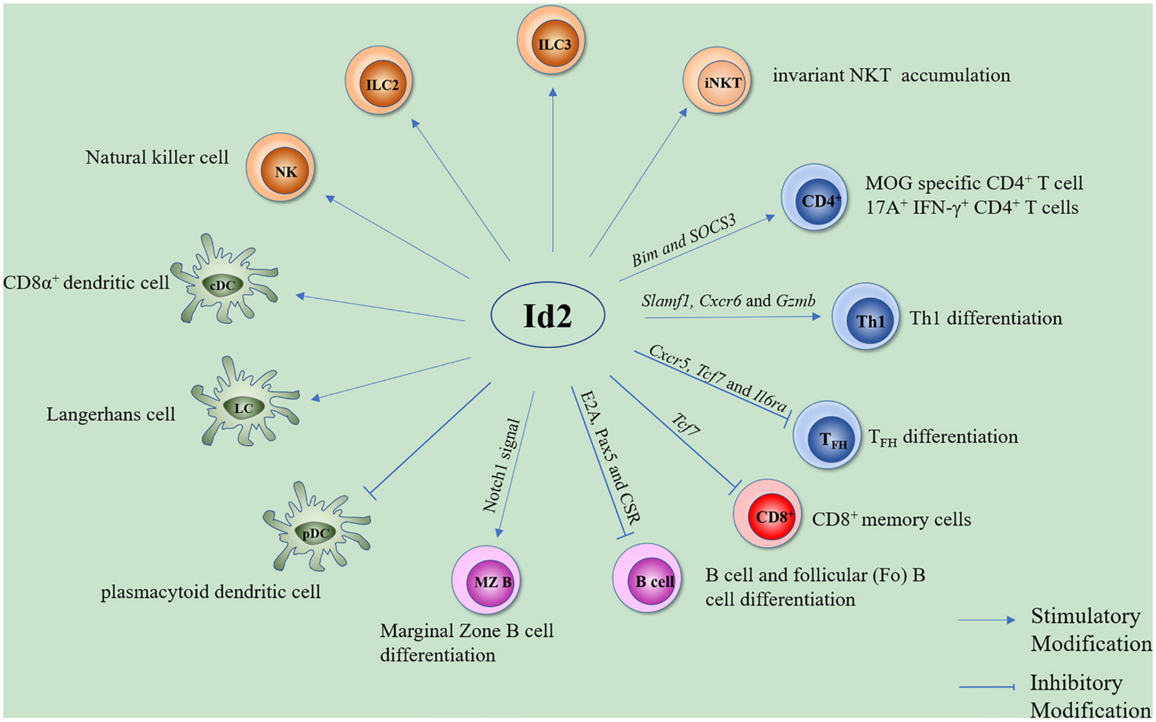


**Fig. 2. Role of Id2 in the differentiation and development of immune cells.** Inhibitor of binding or differentiation 2 (Id2) can promotes T cells activation, Th17 differentiation, but represses the Tfh differentiation, mediates the apoptosis of $CD8^+$T cells and blocks the forming of $CD8^+$ memory T cells. Id2 also acts as a repressor for B cells development and differentiation. During dendritic cell development, Id2 promotes the differentiation of cDCs, contributes to the development of LCs but represses the development of pDCs. Meanwhile, Id2 performs as a driven for the development of Innate Lymphoid Cells.

## 6. Conclusions

Since the discovery of Id2, various evidences suggest that Id2 plays a critical role in the development and differentiation of almost all immune cells. Several studies demonstrate that Id2 seems to be a center of transcriptional factors to control the fate of immune cells. We can find that the mechanism of how Id2 regulating T cells and B cells is clear. While, how Id2 functions precisely in DC and ILC development and differentiation is unclear (Fig. 2). This problem should be further addressed. It is clear that various factors acting as the upstream of Id2 to regulating its expression, but which one acts on Id2 directly and what the exact mechanism is are poorly understood. Furthermore, as E proteins are targets of Id2, how cytokines and factors mediate the balance between Id2 and E proteins during cell development and differentiation remains unclear. Altogether, it is likely that detailed illumination of the changeable expression of Id2 contributes the understanding of development of immune cells and the process of immune reactions.


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## Conflicts of interest

The authors declare that they have no conflict of interest.


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## References


Becker-Herman, S., Lantner, F., Shachar, I., 2002. Id2 negatively regulates B cell differentiation in the spleen. J. Immunol. 168 (11), 5507–5513.
Benezra, R., Davis, R.L., Lockshon, D., Turner, D.L., Weintraub, H., 1990. The protein Id: a negative regulator of helix-loop-helix dna binding proteins. Cell 61 (1), 49–59.
Bernink, J.H., et al., 2013. Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. Nat. Immunol. 14 (3), 221–229.
Boos, M.D., et al., 2007. Mature natural killer cell and lymphoid tissue-inducing cell development requires Id2-mediated suppression of E protein activity. J. Exp. Med. 204 (5), 1119–1130.
Cancro, M.P., 2005. B cells and aging: gauging the interplay of generative, selective, and homeostatic events. Immunol. Rev. 205, 48–59.
Chea, S., et al., 2016. Single-cell gene expression analyses reveal heterogeneous responsiveness of fetal innate lymphoid progenitors to notch signaling. Cell Rep. 14 (6), 1500–1516.
Chopin, M., et al., 2013. Langerhans cells are generated by two distinct PU.1-dependent transcriptional networks. J. Exp. Med. 210 (13), 2967–2980.
Christy, B.A., et al., 1991. An Id-related helix-loop-helix protein encoded by a growth factor-inducible gene. Proc. Natl. Acad. Sci. U. S. A. 88 (5), 1815–1819.
Chung, J.B., Silverman, M., Monroe, J.G., 2003. Transitional B cells: step by step towards immune competence. Trends Immunol. 24 (6), 343–349.
D'Cruz, L.M., et al., 2014. E and Id proteins influence invariant NKT cell sublineage differentiation and proliferation. J. Immunol. 192 (5), 2227–2236.
Delconte, R.B., Shi, Wei, Sathe, P., Ushiki, T., Seillet, C., Minnich, M., Kolesnik, T.B., Rankin, L.C., Mielke, L.A., Zhang, J.G., Busslinger, M., Smyth, M.J., Hutchinson, D.S., Nutt, S.L., Nicholson, S.E., Alexander, W.S., Corcoran, L.M., Vivier, E., Belz, G.T., Carotta, S., Huntington, N.D., 2016. The helix-loop-helix protein ID2 governs NK cell fate by tuning their sensitivity to Interleukin-15. Immunity 44 (1), 103–115.
Diefenbach, A., Colonna, M., Koyasu, S., 2014. Development, differentiation, and diversity of innate lymphoid cells. Immunity 41 (3), 354–365.
Ellenberger, T., et al., 1994. Crystal structure of transcription factor E47: E-box recognition by a basic region helix-loop-helix dimer. Genes Dev. 8 (8), 970–980.
Ellis, H.M., Spann, D.R., Posakony, J.W., 1990. Extramacrochaetae, a negative regulator of sensory organ development in Dr innate lymphoid cellsosophila, defines a new class of helix-loop-helix proteins. Cell 61 (1), 27–38.
Fuchs, A., et al., 2013. Intraepithelial type 1 innate lymphoid cells are a unique subset of IL-12- and IL-15-responsive IFN-gamma-producing cells. Immunity 38 (4), 769–781.
Gascoyne, D.M., Long, Elaine, Veiga-Fernandes, H., de Boer, J., Williams, O., Seddon, B., Coles, M., Kioussis, D., Brady, H.J., 2009. The basic leucine zipper transcription factor E4BP4 is essential for natural killer cell development. Nat. Immunol. 10 (10), 1118–1124.
Ghosh, H.S., et al., 2014. ETO family protein Mtg16 regulates the balance of dendritic cell subsets by repressing Id2. J. Exp. Med. 211 (8), 1623–1635.
Ginhoux, F., et al., 2009. The origin and development of nonlymphoid tissue CD103+ DCs. J. Exp. Med. 206 (13), 3115–3130.
Gonda, H., Sugai, Manabu, Nambu, Y., Katakai, T., Agata, Y., Mori, K.J., Yokota, Y.,

Shimizu, A., 2003. The balance between Pax5 and Id2 activities is the key to AID gene expression. J. Exp. Med. 198 (9).
Gore, Y., et al., 2010. Mad3 negatively regulates B cell differentiation in the spleen by inducing Id2 expression. Mol. Biol. Cell 21 (11), 1864–1871.
Guo, X., Liang, Y., Zhang, Y., Lasorella, A., Kee, B.L., Fu, Y.X., 2015. Innate lymphoid cells control early colonization resistance against intestinal pathogens through ID2-dependent regulation of the microbiota. Immunity 42 (4), 731–743.
Hacker, C., et al., 2003. Transcriptional profiling identifies Id2 function in dendritic cell development. Nat. Immunol. 4 (4), 380–386.
Hashimoto, D., Miller, J., Merad, M., 2011. Dendritic cell and macrophage heterogeneity in vivo. Immunity 35 (3), 323–335.
Heinz, L.X., et al., 2006. Differential involvement of PU.1 and Id2 downstream of TGF-beta1 during Langerhans-cell commitment. Blood 107 (4), 1445–1453.
Iavarone, A., et al., 1994. The helix-loop-helix protein Id-2 enhances cell proliferation and binds to the retinoblastoma protein. Genes Dev. 8 (11), 1270–1284.
Ikawa, T., et al., 2001. Commitment to natural killer cells requires the helix-loop-helix inhibitor Id2. Proc. Natl. Acad. Sci. U. S. A. 98 (9), 5164–5169.
Ippolito, G.C., Dekker, J.D., Wang, Y.H., Lee, B.K., Shaffer 3rd, A.L., Lin, J., Wall, J.K., Lee, B.S., Staudt, L.M., Liu, Y.J., Iyer, V.R., Tucker, H.O., 2014. Dendritic cell fate is determined by BCL11A. Proc. Natl. Acad. Sci. U. S. A. 111 (11), E998–1006.
Jackson, J.T., et al., 2011. Id2 expression delineates differential checkpoints in the genetic program of CD8alpha+ and CD103+ dendritic cell lineages. EMBO J. 30 (13), 2690–2704.
Jaiswal, H., Kaushik, Monika, Sougrat, R., Gupta, M., Dey, A., Verma, R., Ozato, K., Tailor, P., 2013. Batf3 and Id2 have a synergistic effect on Irf8-directed classical CD8α+ dendritic cell development. J. Immunol. 191 (12), 5993–6001.
Jensen, K., Schaffer, Lana, Olstad, O.K., Bechensteen, A.G., Hellebostad, M., Tjønnfjord, G.E., Kierulf, P., Gautvik, K.M., Osnes, L.T., 2010. Striking decrease in the total precursor B-cell compartment during early childhood as evidenced by flow cytometry and gene expression changes. Pediatr. Hematol. Oncol. 27 (1), 31–45.
Jensen, K., Rother, Magdalena B., Brusletto, B.S., Olstad, O.K., Dalsbotten Aass, H.C., van Zelm, M.C., Kierulf, P., Gautvik, K.M., 2013. Increased ID2 levels in adult precursor B cells as compared with children is associated with impaired Ig locus contraction and decreased bone marrow output. J. Immunol. 191 (3), 1210–1219.
Ji, M., et al., 2008. Id2 intrinsically regulates lymphoid and erythroid development via interaction with different target proteins. Blood 112 (4), 1068–1077.
Joan Garrell, J.M., 1990. The Drosophila extramacrochaetae locus, an antagonist of proneural genes that, like these genes, encodes a helix-loop-helix protein. Cell 61 (1), 39–48.
Johnson, K.M., Owen, K., Witte, P.L., 2002. Aging and developmental transitions in the B cell lineage. Int. Immunol. 14 (11), 1313–1323.
Kee, B.L., Quong, Melanie W., Murre, C., 2000. E2A proteins: essential regulators at multiple stages of B-cell development. Immunol. Rev. 175, 138–149.
Khandelwal, P., et al., 2013. Ocular mucosal CD11b+ and CD103+ mouse dendritic cells under normal conditions and in allergic immune responses. PLoS One 8 (5), e64193.
Klein Wolterink, R.G., et al., 2013. Essential, dose-dependent role for the transcription factor Gata3 in the development of IL-5+ and IL-13+ type 2 innate lymphoid cells. Proc. Natl. Acad. Sci. U. S. A. 110 (25), 10240–10245.
Kusunoki, T., et al., 2003. TH2 dominance and defective development of a CD8+ dendritic cell subset in Id2-deficient mice. J. Allergy Clin. Immunol. 111 (1), 136–142.
Li, H., Ji, M., Klarmann, K.D., Keller, J.R., 2010. Repression of Id2 expression by Gfi-1 is required for B-cell and myeloid developmen. Blood 116 (7), 1060–1069.
Li, H.S., et al., 2012. The signal transducers STAT5 and STAT3 control expression of Id2 and E2-2 during dendritic cell development. Blood 120 (22), 4363–4373.
Li, J., et al., 2017. Id2 collaborates with Id3 to suppress invariant NKT and innate-like tumors. J. Immunol. 198 (8), 3136–3148.
Lim, A.W., 2015. M.A., deciphering the transcriptional switches of innate lymphoid cell programming: the right factors at the right time. Genes Immun. 16 (3), 177–186.
Lin, Y.Y., Jones-Mason, Mary E., Inoue, M., Lasorella, A., Iavarone, A., Li, Q.J., Shinohara, M.L., Zhuang, Y., 2012. Transcriptional regulator Id2 is required for the CD4 T cell immune response in the development of experimental autoimmune encephalomyelitis. J. Immunol. 189 (3), 1400–1405.
Loder, F., et al., 1999. B cell development in the spleen takes place in discrete steps and is determined by the quality of B cell receptor-derived signals. J. Exp. Med. 190 (1), 75–89.
Male, V., et al., 2014. The transcription factor E4bp4/Nfil3 controls commitment to the NK lineage and directly regulates Eomes and Id2 expression. J. Exp. Med. 211 (4), 635–642.
Masson, F., et al., 2013. Id2-mediated inhibition of E2A represses memory CD8+ T cell differentiation. J. Immunol. 190 (9), 4585–4594.
Masson, F., et al., 2014. Id2 represses E2A-mediated activation of IL-10 expression in T cells. Blood 123 (22), 3420–3428.
Mathas, S., et al., 2006. Intrinsic inhibition of transcription factor E2A by HLH proteins ABF-1 and Id2 mediates reprogramming of neoplastic B cells in Hodgkin lymphoma. Nat. Immunol. 7 (2), 207–215.
Matthias, P., Rolink, A.G., 2005. Transcriptional networks in developing and mature B cells. Nat. Rev. Immunol. 5 (6), 497–508.
McKenzie, A.N., Spits, H., Eberl, G., 2014. Innate lymphoid cells in inflammation and immunity. Immunity 41 (3), 366–374.
Mercer, E.M., et al., 2011. Multilineage priming of enhancer repertoires precedes commitment to the B and myeloid cell lineages in hematopoietic progenitors. Immunity 35 (3), 413–425.
Miyazaki, M., et al., 2014. Id2 and Id3 maintain the regulatory T cell pool to suppress inflammatory disease. Nat. Immunol. 15 (8), 767–776.
Miyazaki, M., Miyazaki, Kazuko, Chen, S., Chandra, V., Wagatsuma, K., Agata, Y., Rodewald, H.R., Saito, R., Chang, A.N., Varki, N., Kawamoto, H., Murre, C., 2015. The E-Id protein axis modulates the activities of the PI3K-AKT-mTORC1-Hif1a and c-myc/p19Arf pathways to suppress innate variant TFH cell development, thymocyte expansion, and lymphomagenesis. Genes Dev. 29 (4), 409–425.
Monticelli, L.A., et al., 2009. Transcriptional regulator Id2 controls survival of hepatic NKT cells. Proc. Natl. Acad. Sci. U. S. A. 106 (46), 19461–19466.
Moro, K., et al., 2010. Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. Nature 463 (7280), 540–544.
Mowel, W., et al., 2017. Group 1 innate lymphoid cell lineage identity is determined by a cis-regulatory element marked by a long non-coding RNA. Immunity 47 (3), 435–449 e8.
Nagasawa, M., et al., 2008. Development of human plasmacytoid dendritic cells depends on the combined action of the basic helix-loop-helix factor E2-2 and the Ets factor Spi-B. Eur. J. Immunol. 38 (9), 2389–2400.
Nagasawa, M., et al., 2017. Human CD5(+) innate lymphoid cells are functionally immature and their development from CD34(+) progenitor cells is regulated by Id2. Front. Immunol. 8, 1047.
Nandakumar, V., et al., 2013. Epigenetic control of natural killer cell maturation by histone H2A deubiquitinase, MYSM1. Proc. Natl. Acad. Sci. U. S. A. 110 (41), E3927–E3936.
Omilusik, K.D., et al., 2018. Sustained Id2 regulation of E proteins is required for terminal differentiation of effector CD8(+) T cells. J. Exp. Med. 215 (3), 773–783.
Pelanda, R., Torres, R.M., 2012. Central B-cell tolerance: where selection begins. Cold Spring Harb. Perspect. Biol. 4 (4) p. a007146.
Pongubala, J.M., et al., 2008. Transcription factor EBF restricts alternative lineage options and promotes B cell fate commitment independently of Pax5. Nat. Immunol. 9 (2), 203–215.
Riechmann, V., van Crüchten, I., Sablitzky, F., 1994. The expression pattern of Id4, a novel dominant negative helix-loop-helix protein, is distinct from Id1, Id2 and Id3. Nucleic Acids Res. 22 (5), 749–755.
Rossi, M.I., Yokota, T., Medina, K.L., Garrett, K.P., Comp, P.C., 2003. Schipul AH Jr, Kincade PW, B lymphopoiesis is active throughout human life, but there are developmental age-related changes. Blood 101 (2), 576–584.
Satoh-Takayama, N., et al., 2010. IL-7 and IL-15 independently program the differentiation of intestinal CD3-NKp46+ cell subsets from Id2-dependent precursors. J. Exp. Med. 207 (2), 273–280.
Schlitzer A, Loschko, J., Mair, K., Vogelmann, R., Henkel, L., Einwächter, H., Schiemann, M., Niess, J.H., Reindl, W., Krug, A., 2011. Identification of CCR9- murine plasmacytoid DC precursors with plasticity to differentiate into conventional DCs. Blood 117 (24), 6562–6570.
Schotte R, D.W., Nagasawa, M., Yasuda, Y., Bakker, A.Q., Spits, H., Blom, B., 2010. Synergy between IL-15 and Id2 promotes the expansion of human NK progenitor cells, which can be counteracted by the E protein HEB required to drive T cell development. J. Immunol. 184 (12), 6670–6679.
Scott, C.L., et al., 2016. The transcription factor Zeb2 regulates development of conventional and plasmacytoid DCs by repressing Id2. J. Exp. Med. 213 (6), 897–911.
Seillet, C., Jackson, Jacob T., Markey, K.A., Brady, H.J., Hill, G.R., Macdonald, K.P., Nutt, S.L., Belz, G.T., 2013. CD8α+ DCs can be induced in the absence of transcription factors Id2, Nfil3, and Batf3. Blood 121 (9), 1574–1583.
Sere, K., et al., 2012. Two distinct types of Langerhans cells populate the skin during steady state and inflammation. Immunity 37 (5), 905–916.
Shaw, L.A., et al., 2016. Id2 reinforces TH1 differentiation and inhibits E2A to repress TFH differentiation. Nat. Immunol. 17 (7), 834–843.
Sikder, H., et al., 2003. Disruption of Id1 reveals major differences in angiogenesis between transplanted and autochthonous tumors. Cancer Cell 4 (4), 291–299.
Spits, H., Couwenberg, F., Bakker, A.Q., Weijer, K., Uittenbogaart, C.H., 2000. Id2 and Id3 inhibit development of CD34(+) stem cells into predendritic cell (pre-DC)2 but not into pre-DC1. Evidence for a lymphoid origin of pre-DC2. J. Exp. Med. 192 (12), 1775–1784.
Sugai, M., Gonda, H., Kusunoki, T., Katakai, T., Yokota, Y., Shimizu, A., 2003. Essential role of Id2 in negative regulation of IgE class switching. Nat. Immunol. 4 (1), 25–30.
Sugai, M., Gonda, Hiroyuki, Nambu, Y., Yokota, Y., Shimizu, A., 2004. Role of Id proteins in B lymphocyte activation: new insights from knockout mouse studies. J. Mol. Med. 82 (9), 592–599.
Sun, X.H., Copeland, Neal, Jenkins, N.A., Baltimore, D., 1991. Id proteins Id1 and Id2 selectively inhibit DNA binding by one class of helix-loop-helix proteins. Mol. Cell. Biol. 11 (11), 5603–5611.
Thal, M.A., Carvalho, T.L., He, T., Kim, H.G., Gao, H., Hagman, J., Klug, C.A., 2009. Ebf1-mediated down-regulation of Id2 and Id3 is essential for specification of the B cell lineage. Proc. Natl. Acad. Sci. U. S. A. 106 (2), 552–557.
Verykokakis, M., et al., 2013. Essential functions for ID proteins at multiple checkpoints in invariant NKT cell development. J. Immunol. 191 (12), 5973–5983.
Weigert, A., Weichand, B., Sekar, D., Sha, W., Hahn, C., Mora, J., Ley, S., Essler, S., Dehne, N., Brüne, B., 2012. HIF-1α is a negative regulator of plasmacytoid DC development in vitro and in vivo. Blood 120 (15), 3001–3006.
Wong, S.H., Walker, J.A., Jolin, H.E., Drynan, L.F., Hams, E., Camelo, A., Barlow, J.L., Neill, D.R., Panova, V., Koch, U., Radtke, F., Hardman, C.S., Hwang, Y.Y., Fallon, P.G., McKenzie, A.N., 2012. Transcription factor RORα is critical for nuocyte development. Nat. Immunol. 13 (3), 229–236.
Xu, W., et al., 2015. NFIL3 orchestrates the emergence of common helper innate lymphoid cell precursors. Cell Rep. 10 (12), 2043–2054.
Yokota, Y., et al., 1999. Development of peripheral lymphoid organs and natural killer cells depends on the helix-loop-helix inhibitor Id2. Nature 397 (6721), 702–706.
Zebedee, Z., Hara, E., 2001. Id proteins in cell cycle control and cellular senescence. Oncogene 20 (58), 8317–8325.
Zhang, P., Zhao, Y., Sun, X.H., 2013. Notch-regulated periphery B cell differentiation involves suppression of E protein function. J. Immunol. 191 (2), 726–736.