Homeostatic Regulation of Intestinal Macrophages by the Transcription Factor IRF-2

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Intestinal macrophages are crucial for maintaining mucosal immune homeostasis. However, the molecular mechanisms regulating their development remain largely unexplored. Here, I demonstrate that interferon regulatory factor 2 (IRF-2) is an essential transcription factor for intestinal macrophage homeostasis. Using IRF-2-deficient mice, I identified that IRF-2 is required for the maintenance of distinct colonic macrophage subsets. Notably, IRF-2 loss severely impaired $CD4^+Tim4^+$ macrophage development in a type I IFN-independent manner, whereas $CD4^+Tim4^-$ subset exhibited a type I IFN-dependent defect, at least in part. These findings suggest that IRF-2 regulates macrophage development via both type I IFN-dependent and -independent mechanisms. This study provides novel insights into the transcriptional regulation of intestinal macrophages and their role in mucosal immunity. *Shinshu Med J 73 : 223—233, 2025*

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I Introduction

Mucosal tissues, including the gastrointestinal, respiratory, and urogenital tracts, serve as the primary interface between the host and the external environment, constantly exposed to diverse microorganisms, dietary antigens, and environmental factors. In this complex milieu, the immune system must finely tune the balance between protective immune responses and immune tolerance[1)2)]. Mucosal immunity is orchestrated by both innate and adaptive immune cell populations. Among these, Peyer's patches, a type of secondary lymphoid tissue, and the lamina propria, though not classified as a lymphoid organ, play pivotal roles in the gut-associated immune system. In particular, the lamina propria harbors not only lymphocytes but also a diverse array of immune cells, including dendritic cells (DCs), macrophages, and neutrophils, making it the "largest immune organ" in the body. Intestinal macrophages, in particular, play a central role in maintaining tissue homeostasis and defending against pathogens[3)-5)]. While possessing high phagocytic activity, they exhibit a unique ability to limit the excessive production of pro-inflammatory cytokines in response to commensal bacteria, thereby preventing unnecessary inflammatory responses[6)-8)]. Moreover, previous reports have identified a heterogeneous population of intestinal macrophages, which can be classified based on their developmental origins[9)-11)]. These findings highlight the crucial roles of macrophages in mucosal immunity, particularly in immune surveillance, tolerance, and inflammation control. Further elucidation of these regulatory mechanisms may contribute to the development of novel therapeutic strategies for inflammatory bowel disease and other mucosal immune disorders.

Interferon regulatory factor-2 (IRF-2) is a critical transcription factor that regulates the balance of immune responses. It primarily functions as a negative regulator of type I interferon signaling, suppressing excessive type I interferon responses to prevent

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chronic inflammation and autoimmune diseases[12)13)]. In addition, IRF-2 has been shown to play a key role in regulating various immune systems including T cell development and responses, dendritic cell differentiation, and innate lymphoid cell development[14)-20)]. Thus, IRF-2 is an essential transcription factor for maintaining immune homeostasis, and elucidating its regulatory mechanisms may contribute to the development of therapeutic strategies for immune-related diseases. However, the precise functions and roles of IRF-2 in the mucosal immune system, especially in intestinal macrophages, remain largely unexplored.

In this study, I demonstrate that IRF-2 plays a crucial role in the development of intestinal macrophages. In mice with IRF-2 deficiency, developmental impairments were observed across distinct subsets of intestinal macrophages. Notably, these impairments exhibited subset-specific dependencies on type I interferon signaling. These findings reveal a previously unrecognized role of IRF-2 in macrophage regulation within the mucosal immune system, providing new insights into its contribution to intestinal immune homeostasis.

Ⅱ Materials and Methods

A Mice

Irf2$^{-/-}$ and *Ifnar1*$^{-/-}$ mice, all on a C57BL/6 background as described previously[14)], were used in this study. *Irf2*$^{+/+}$ or *Irf2*$^{+/-}$ mice were used as controls without discrimination. All animals were housed under a specific pathogen-free (SPF) condition at the Shinshu University Animal Facility and handled in accordance with protocols approved by the Shinshu University Committee for Animal Experiments.

B Cell isolation

Isolation of cells from the colons was performed as described previously with some modification[21)]. Briefly, adult (12-week-old) and young (4-week-old) mice were euthanized and isolated colons were cut, opened longitudinally and washed with excess PBS to remove stools and mucus, followed by incubation for 30 min at 37 ℃ with vigorous shaking in 1×PBS supplemented with 5 mM EDTA and 1 mM DTT to remove epithelial layer. Remaining tissues (lamina propria and muscularis) were minced and digested for 30 min at 37 ℃ with gentle shaking in RPMI1640 medium supplemented with 2 % FBS, 0.5 mg/ml Collagenase IV (SIGMA) and 50 U/ml DNase I (Wako). Cells were extensively washed with 1×PBS and resuspended in FACS buffer (1×PBS supplemented with 0.5 % BSA and 2 mM EDTA) and stored at 4 ℃ until further use.

C Flow cytometry

Single-cell suspensions were prepared for cell surface staining with antibodies. The following fluorochrome-conjugated antibodies were used: CD11b (M1/70), CD64 (X54-5/7.1), CX3CR1 (SA011F11), Ly6C (HK1.4), Ly6G (1A8), and Tim4 (RMT4-54) (all from BioLegend); CD4 (GK1.5) and CD45 (30-F11) (ThermoFisher); Fc block (CD16/32, 2.4G2), prepared from culture supernatants of hybridoma, was used. Propidium iodide (PI, Sigma) was used to stain dead cells. Stained cells were analyzed by flow cytometry using FACSCelesta (BD Biosciences), and data were processed with Kaluza software (Beckman Coulter).

D Statistics

An unpaired two-tailed t-test was used to evaluate statistical significance. P values<0.05 were considered statistically significant. Statistical analyses were performed using GraphPad Prism software.

Ⅲ Results

A Impact of IRF2 deficiency on colonic macrophages

To investigate the impact of IRF2 on resident macrophages in the colon under steady-state conditions, I employed IRF2-deficient mice (*Irf2*$^{-/-}$ mice, hereafter referred to as IRF-2$^{-/-}$ mice) and control mice (*Irf2*$^{+/+}$ or *Irf2*$^{+/-}$ mice, hereafter referred to as control mice). Previous reports have shown that intestinal macrophages (CD45$^+$CD64$^+$CD11b$^+$CX3CR1$^+$) can be classified into at least three distinct subsets based on differences in cell surface marker expression: (1) CD4$^+$Tim4$^+$, (2) CD4$^+$Tim4$^-$, and (3) CD4$^-$Tim4$^-$[10)11)] **(Fig. 1A)**. Furthermore, it has been established that CD4$^+$Tim4$^+$ macrophages originate from fetal-derived precursors, whereas CD4$^+$Tim4$^-$ and CD4$^-$Tim4$^-$ macrophages are derived from hematopoietic stem cells postnatally[10)11)]. Tim4 is well-known to be a receptor expressed in certain tissue-resident macrophages

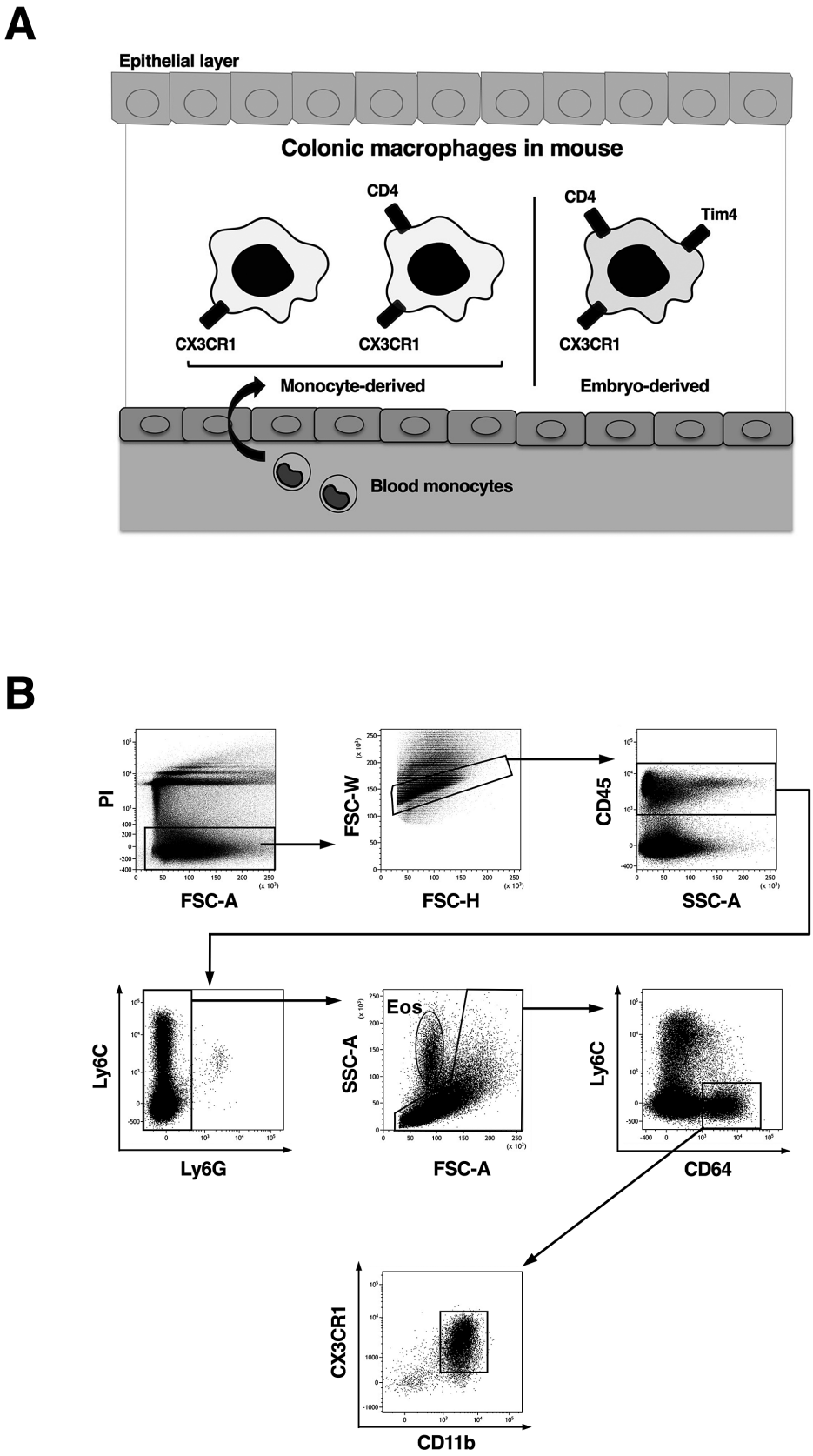

Fig. 1 Schematic diagram of intestinal macrophage subsets in mouse and gating strategy for detection of colonic macrophages in CD45^{+} leukocytes.
(A) Three different macrophage subsets are depicted. (B) PI : propidium iodide, FSC : forward scatter, SSC : side scatter, Eos : eosinophils.

that recognizes phosphatidylserine exposed on the cell surface during apoptosis and plays a role in the engulfment of dead cells[22]. Based on these criteria, I compared colonic macrophages between adult control and IRF-2$^{-/-}$ mice. Initial observations of the colons from both adult mouse groups revealed no overt pathological signs. I isolated cells from colonic tissues after removing the epithelial layer, thereby obtaining populations from the lamina propria and muscularis layers. CD45^{+} cells within the isolated cell populations were analyzed by flow cytometry following a gating strategy **(Fig. 1B)**. Compared to control mice, IRF-2$^{-/-}$ mice exhibited a significant reduction in the total number of CD45^{+} cells **(Fig. 2A)**. Next, using the gating strategy shown in **Fig. 1B**, I compared the relative proportion of macrophages within the CD45^{+} population between control and IRF-2$^{-/-}$ mice. No significant difference was observed in the relative proportion of macrophages. However, the absolute number of macrophages was significantly reduced in IRF-2$^{-/-}$ mice compared to controls **(Fig. 2C)**. These findings suggest an active role for IRF-2 in maintaining colonic macrophage homeostasis.

B IRF-2 is crucial for the development of macrophage subsets in the colon

Next, utilizing the above classification, I investigated the relationship between IRF2 and each macrophage subset in the colon. Strikingly, adult IRF-2$^{-/-}$ mice, compared to adult control mice, exhibited a dramatic reduction in both the proportion and absolute number of CD4^{+}Tim4^{+} macrophages **(Fig. 3A, B)**. Similarly, CD4^{+}Tim4^{-} macrophages also showed a marked reduction in both proportion and absolute number in IRF-2$^{-/-}$ mice **(Fig. 3A, C)**. In contrast, the proportion of CD4^{-}Tim4^{-} macrophages was significantly increased in IRF-2$^{-/-}$ mice compared to controls **(Fig. 3A, D)**. These findings highlight the indispensable role of IRF-2 in maintaining the homeostasis of distinct colonic macrophage subsets.

C Effect of IRF2 on CD4^{+}Tim4^{+} macrophage development in the colon in young mice

As previously reported, CD4^{+}Tim4^{+} macrophages originate from fetal precursors and are established before the onset of bone marrow hematopoiesis, which serves as the primary source of hematopoietic replenishment after birth[10)11)]. To investigate this further, I focused on young mice (4 weeks old) and performed a comparative analysis of CD4^{+}Tim4^{+} macrophages in the colon. As expected, a significant reduction in this subset was observed in IRF-2$^{-/-}$ mice compared to control mice **(Fig. 4A, B)**. Furthermore, an age-related increase in CD4^{+}Tim4^{+} macrophages was observed in control mice but not in IRF-2$^{-/-}$ mice when comparing young and adult mice **(Fig. 4C)**. These findings underscore the pivotal role of the transcription factor IRF2 in the early phase of CD4^{+}Tim4^{+} macrophage development.

D Type I Interferon signaling dependency in the developmental defects of colonic macrophages in IRF2-deficient mice

IRF2 is known to function as a critical regulatory factor in various immune cells, among which its role as a negative regulator of type I interferon signaling has been well established. This negative regulation is crucial for maintaining immune homeostasis[14)-16)]. Given this, I investigated whether the developmental impairment observed in colonic macrophages of IRF-2$^{-/-}$ mice was attributable to dysregulated type I interferon signaling. To address this question, I generated IRF-2$^{-/-}$ mice with IFNαRI deficiency (*Irf2*$^{-/-}$ *Ifnar1*$^{-/-}$ mice, hereafter referred to as IRF-2$^{-/-}$IFNAR1$^{-/-}$ mice) and analyzed the development of colonic macrophages in adult mice in the absence of type I interferon signaling. No significant differences were observed between control and IFNαRI-deficient mice (*Ifnar1*$^{-/-}$ mice, hereafter referred to as IFNAR1$^{-/-}$ mice). However, compared to IFNAR1$^{-/-}$ mice as controls, IRF-2$^{-/-}$ IFNAR1$^{-/-}$ mice exhibited a marked reduction in both the proportion and absolute number of CD4^{+}Tim4^{+} macrophages, resembling the phenotype observed in IRF-2$^{-/-}$ mice **(Fig. 5A, B)**. Interestingly, the absolute number of CD4^{+}Tim4^{-} macrophages in IRF-2$^{-/-}$ IFNAR1$^{-/-}$ mice showed partial but significant recovery compared to IFNAR1$^{-/-}$ mice **(Fig. 5A, Fig. 5C, right panel)**. In contrast, the proportion of CD4^{+}Tim4^{-} macrophages among total macrophages showed a trend toward recovery, though the difference was not statistically significant **(Fig.**

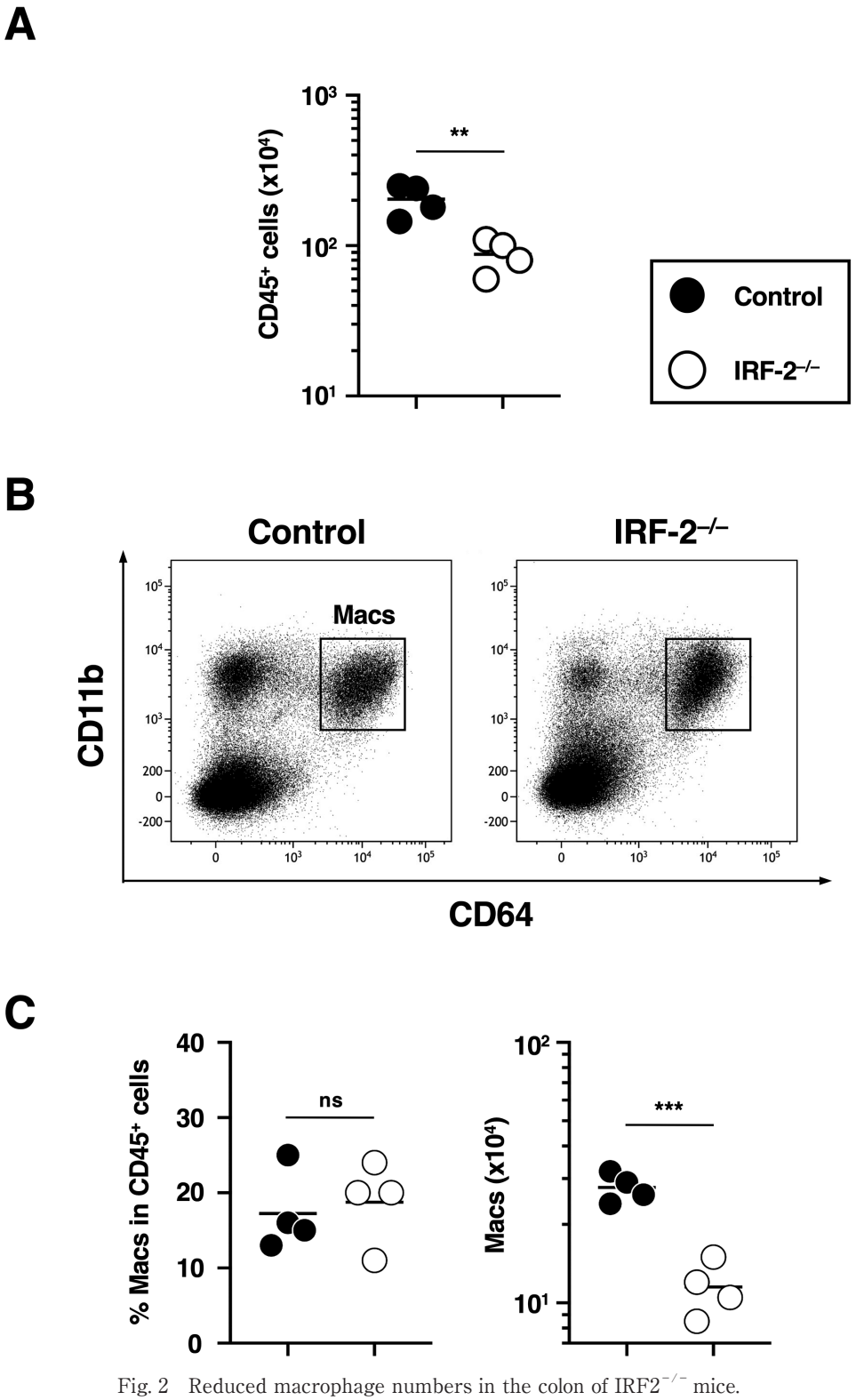

Fig. 2 Reduced macrophage numbers in the colon of IRF2$^{-/-}$ mice.

Flow cytometric analyses were performed using colonic samples of adult mice. (A) Absolute number of CD45^{+} cells in the colon after epithelial layer removal. Dots represent individual mice. Results are pooled from four independent experiments (n = 4 in each mouse group). (B and C) Analysis of total colonic macrophages (Macs : CD11b^{+}CD64^{+}) within CD45^{+} cells in the colon after epithelial layer removal. (B) The plots are representative of four independent experiments. (C) Proportions of Macs within the CD45^{+} cell population and their absolute numbers. Dots represent individual mice. Results are pooled from at least four independent experiments (n = 4 in each mouse group). $^{**}P < 0.01$, $^{***}P < 0.001$, and ns : not significant (unpaired two-tailed t tests).

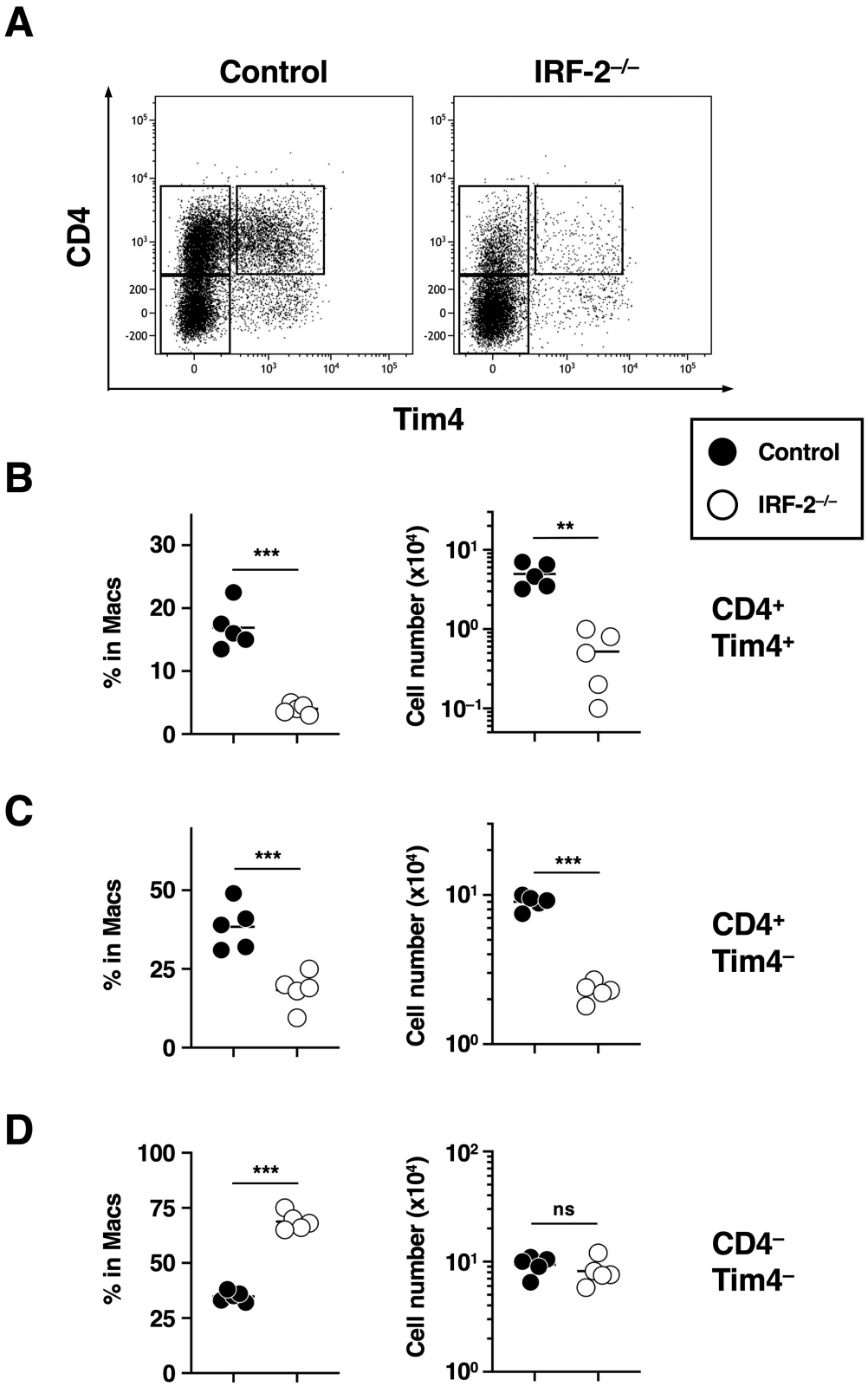

Fig. 3 IRF-2 is crucial for the development of macrophage subsets in the colon.

(A to D) Flow cytometric analysis of each subset within the colonic macrophage (Macs) population ($CD45^+CD64^+CD11b^+CX3CR1^+$) after depletion of $Ly6G^+$, $Ly6C^+$, and eosinophil populations in adult mice. (A) The plots are representative of at least three independent experiments. (B to D) Proportions and absolute numbers of each macrophage subset. Dots represent individual mice. Results are pooled from at least three independent experiments (n = 5 in each mouse group). $^{**}P<0.01$, $^{***}P<0.001$, and ns : not significant (unpaired two-tailed t tests).

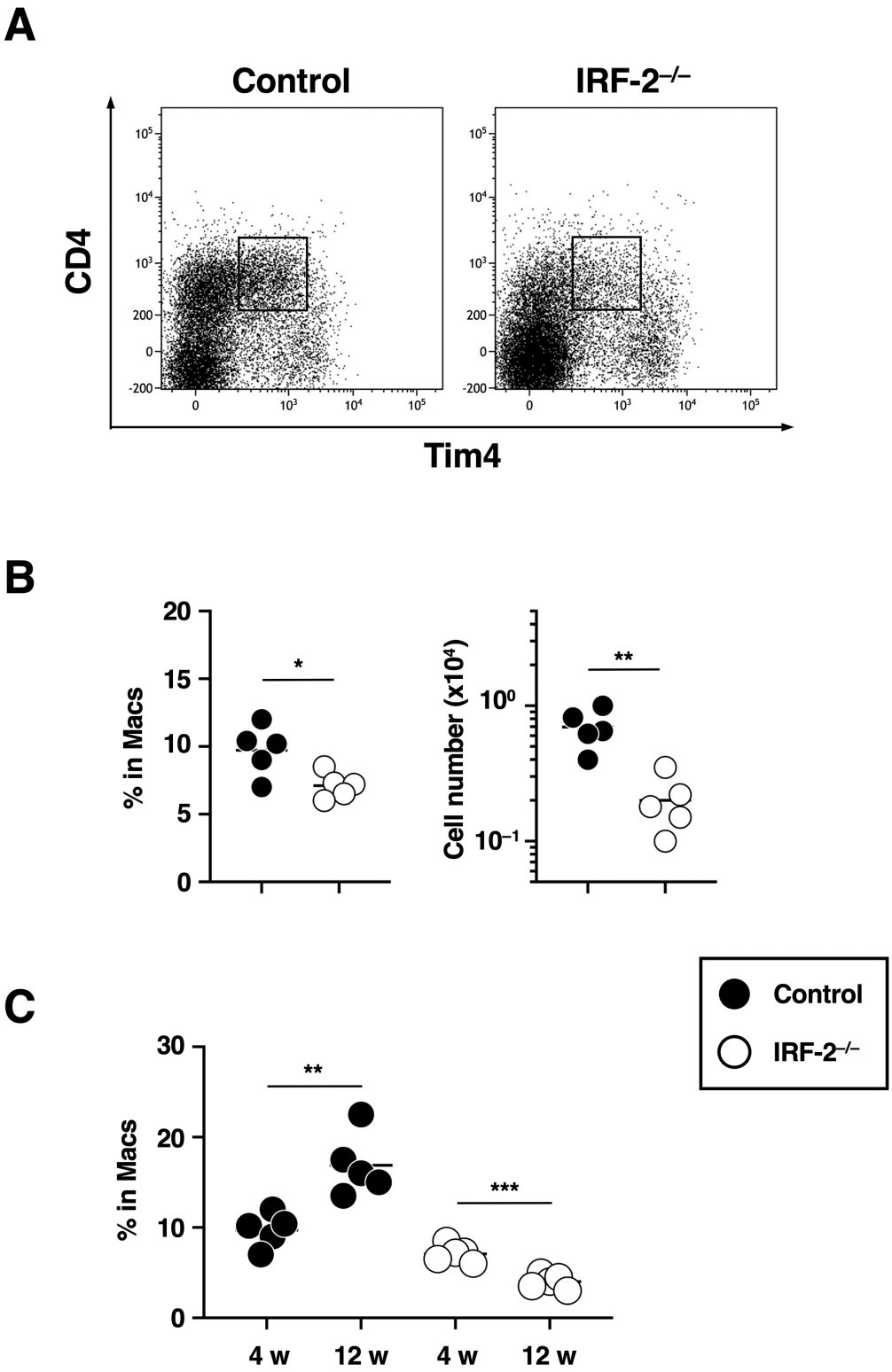

Fig. 4 Effect of IRF2 on $CD4^+Tim4^+$ macrophage development in the colon in young mice.

(A and B) Flow cytometric analysis of $CD4^+Tim4^+$ macrophages within the colonic macrophage (Macs) population ($CD45^+CD64^+CD11b^+CX3CR1^+$) after depletion of $Ly6G^+$, $Ly6C^+$, and eosinophil populations in young mice. (A) The plots are representative of at least three independent experiments. (B) Proportions and absolute numbers of $CD4^+Tim4^+$ macrophages. Dots represent individual mice. Results are pooled from at least three independent experiments (n = 5 in each mouse group). (C) Comparison of the proportions of $CD4^+Tim4^+$ macrophages within the Macs population between young (4-week-old ; 4 w) and adult (12-week-old ; 12 w) mice. Note that the presented data is a combination of Fig. 3B and Fig. 4B. $^*P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, and $^{****}P<0.0001$ (unpaired two-tailed t tests).

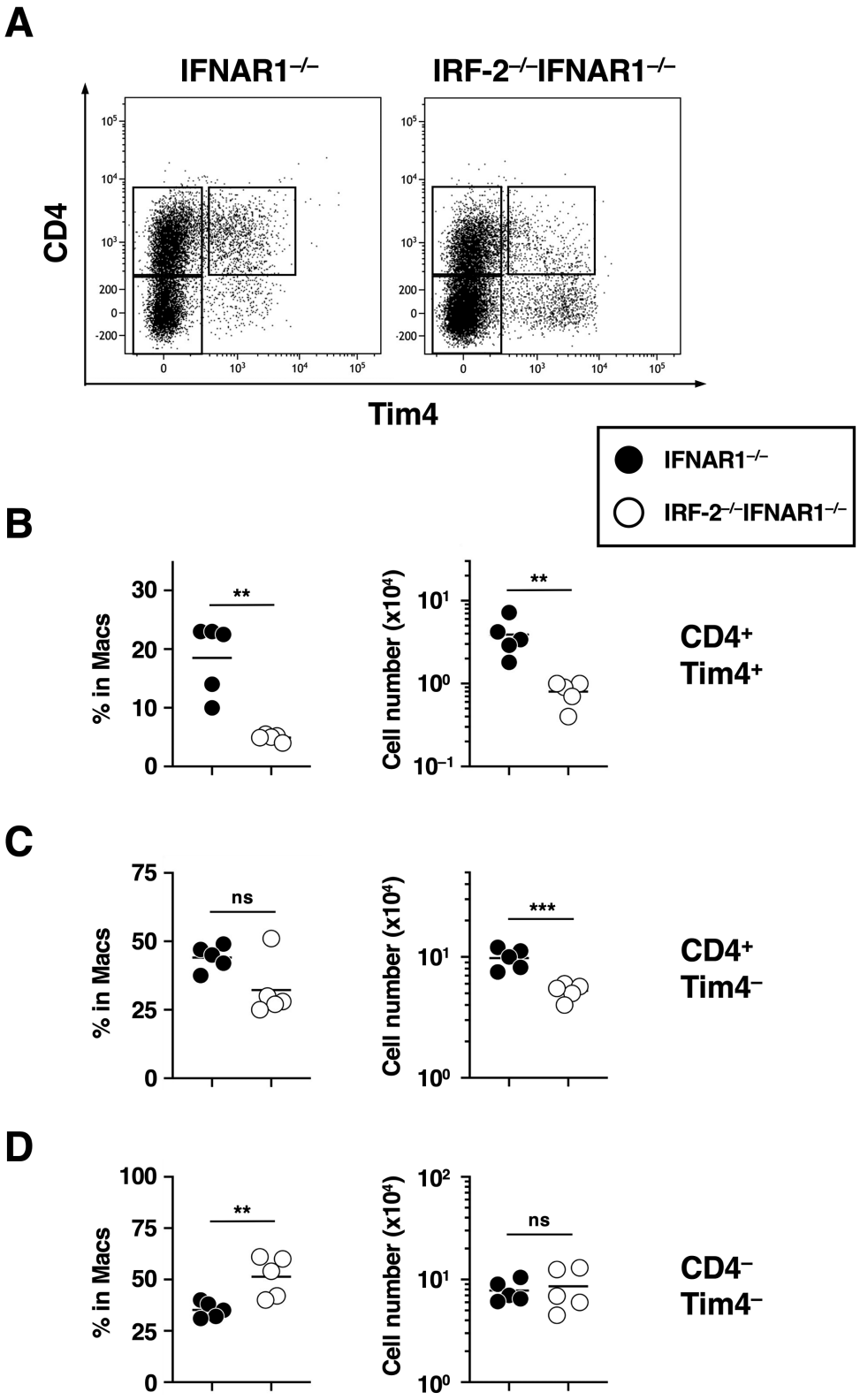

Fig. 5 Type I Interferon signaling dependency in the developmental defects of colonic macrophages in IRF2-deficient mice.

(A to D) Flow cytometric analysis of each subset within the colonic macrophage (Macs) populations ($CD45^+CD64^+CD11b^+CX3CR1^+$) after depletion of $Ly6G^+$, $Ly6C^+$, and eosinophil populations in adult mice. (A) The plots are representative of at least three independent experiments. (B to D) Proportions and absolute numbers of each macrophage subset. Dots represent individual mice. Results are pooled from at least three independent experiments (n = 5 in each mouse group). $^{**}P<0.01$, $^{***}P<0.001$, and ns : not significant (unpaired two-tailed t tests).

5C, left panel). Additionally, the proportion of $CD4^-Tim4^-$ macrophages among total macrophages was significantly altered **(Fig. 5D, left panel)**. When compared with the findings in IRF-$2^{-/-}$ mice **(Fig. 3D)**, the increase in $CD4^+Tim4^-$ macrophages **(Fig. 5C)** appeared to be accompanied by a reduction in the proportion of $CD4^-Tim4^-$ macrophages. This trend was also confirmed in terms of absolute cell numbers **(Fig. 5D, right panel)**.

Collectively, these results indicate that the developmental impairment of colonic $CD4^+Tim4^+$ macrophages in IRF-$2^{-/-}$ mice occurs independently of type I interferon signaling. In contrast, the development of both colonic $CD4^+Tim4^-$ and $CD4^-Tim4^-$ macrophages is at least partially dependent on type I interferon signaling.

Ⅳ Discussion

Since the identification of intestinal tissue-resident macrophages, extensive research has been conducted worldwide to elucidate their function. However, the molecular mechanisms governing their differentiation and maturation remain largely unknown. In this study, I identified for the first time that the transcription factor IRF-2, which is known to regulate various immune cells, plays a crucial role in the establishment of the colonic macrophage population. Given the limited knowledge of the molecular regulators that control the development of intestinal tissue-resident macrophages, the findings of this study provide significant insights into this field.

In the colon, particularly in the lamina propria and muscularis layers (excluding the intestinal epithelial layer), IRF-$2^{-/-}$ mice exhibited a significant reduction in leukocyte numbers compared to control mice. However, this reduction does not appear to be specific to macrophages. Indeed, previous studies have reported a marked depletion of innate lymphoid cells in the intestines of IRF-$2^{-/-}$ mice[18]. Furthermore, the significant decrease in the absolute number of colonic macrophages within the leukocyte population suggests that IRF-2 is essential for maintaining the colonic macrophage pool size.

Recent studies have classified intestinal macrophages into distinct subsets[10)11)]. In this study, I demonstrated that IRF-2 plays a critical role in the development of these subsets, highlighting the importance of the transcriptional regulation by IRF-2 in colonic macrophages. Notably, I observed a severe developmental defect of $CD4^+Tim4^+$ colonic macrophages, which originate from embryonic progenitors, in IRF-$2^{-/-}$ mice. In general, many tissue-resident macrophages-such as microglia, Langerhans cells in the skin, alveolar macrophages in the lungs, Kupffer cells in the liver, and large peritoneal macrophages-originate from the yolk sac and fetal liver, migrate to their respective tissues, and establish residency through interactions with the local tissue environment, thereby contributing to tissue homeostasis[23)24)]. The precise developmental stage at which $CD4^+Tim4^+$ macrophages fail to develop in IRF-$2^{-/-}$ mice remains unclear. However, I observed a significant reduction in $CD4^+Tim4^+$ macrophages in young IRF-$2^{-/-}$ mice compared to control mice, suggesting that IRF-2 is involved in the early-stage regulation of this macrophage subset's development.

Moreover, the marked reduction in this subset in IRF-$2^{-/-}$ mice was found to be independent of type I interferon signaling. This finding suggests that $CD4^+Tim4^+$ macrophages undergo differentiation and maturation through a mechanism independent of type I interferon signaling. Given that the regulatory factors controlling this subset remain unidentified, future studies should aim to elucidate the upstream and downstream regulators of IRF-2 in this context.

This study also revealed that IRF-2 is involved in the maintenance of the $CD4^+Tim4^-$ macrophage subset. Unlike $CD4^+Tim4^+$ macrophages, this subset primarily originates from bone marrow-derived hematopoiesis after birth, which is consistent with previous reports[10)11)]. The developmental relationship between $CD4^+Tim4^-$ and $CD4^-Tim4^-$ macrophage subsets remains unclear. However, analysis using IRF-$2^{-/-}$ mice implies that $CD4^-Tim4^-$ macrophages differentiate into $CD4^+Tim4^-$ macrophages. Furthermore, type I interferon signaling appears to negatively regulate this differentiation process. These findings support a model in which IRF-2 promotes

macrophage differentiation by suppressing type I interferon signaling in intestinal macrophages. On the other hand, the loss of type I interferon signaling did not fully rescue the defective development of $CD4^+$ $Tim4^-$ macrophages in IRF-$2^{-/-}$ mice. This result suggests the existence of an unknown factor essential for IRF-2-mediated regulation of either the differentiation from $CD4^-Tim4^-$ to $CD4^+Tim4^-$ macrophages or the survival of $CD4^+Tim4^-$ macrophages. Identifying such regulatory factors remains an important objective for future research.

In summary, this study demonstrates that the transcription factor IRF2 plays an essential role in the homeostatic regulation of intestinal macrophages. However, it remains unclear how IRF2 deficiency in macrophages contributes to intestinal diseases. Further detailed analyses are required to elucidate the roles of individual macrophage subsets in host defense and the impact of IRF2 on these functions.

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