別紙４

研究成果の刊行に関する一覧表レイアウト

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# α(1,3) Fucosyltransferases IV and VII Are Essential for the Initial Recruitment of Basophils in Chronic Allergic Inflammation

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Basophils act as initiator cells for the development of IgE-mediated chronic allergic inflammation (IgE-CAI). However, detailed mechanisms of initial recruitment of basophils into the skin have yet to be clarified. Selectins mediate leukocyte capture and rolling on the vascular endothelium for extravasation. Counter-receptor activity of selectins is regulated by α(1, 3) fucosyltransferases (FTs) IV and VII. To clarify the contribution of selectin ligands regulated by FTs for initial basophil recruitment, IgE-CAI was induced in mice deficient in *FT-IV* and/or *FT-VII* genes. Although FT-IV(−/−) and FT-VII(−/−) mice exhibited comparable skin responses to wild-type mice, the FT-IV(−/−)/FT-VII(−/−) mice showed significantly impaired inflammation. Although the transfer of basophils to FcRγ(−/−) mice induced IgE-CAI, this induction was completely absent when basophils from FT-IV(−/−)/FT-VII(−/−) mice were transferred. L-selectin, but not P- and E-selectin, blocking Abs inhibited skin inflammation *in vivo*. P-selectin glycoprotein-1 (PSGL-1) antibody also ameliorated skin inflammation, and basophils were bound to L-selectin in a PSGL-1-dependent manner, which was regulated by FT-IV/VII. Functional PSGL-1 generated by basophil FT-IV/VII and its subsequent binding to L-selectin could be one of the essential steps required for initial basophil recruitment and the development of IgE-CAI in mice.

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## INTRODUCTION

Leukocyte recruitment from the vasculature to the inflammatory sites is a multistep process. The first step of extravasation is leukocyte capture and rolling along the endothelial surfaces, a process that is mediated by selectins. P- and E-selectins on the endothelial cells contribute to the primary capture of leukocytes via binding to their ligands. Conversely, L-selectin is constitutively expressed on most types of circulating leukocytes. L-selectin binds to its ligands on activated endothelial cells (Spertini *et al.*, 1992; Luscinskas *et al.*, 1994; Tu *et al.*, 1999), and also mediates binding to leukocytes already adhering to endothelial cells (secondary capture) (Guyer *et al.*, 1996; Walcheck *et al.*, 1996).

The glycans that contribute to selectin counter-receptor activity arise through glycosylation reactions in which the terminal steps are catalyzed by α(1,3) fucosyltransferases (FTs) (Lowe, 2002). Mice deficient in the *FT-VII* gene (FT-VII(−/−) mice) are characterized by absent P-, E-, and L-selectin ligand activities (Maly *et al.*, 1996). Although the contribution of FT-IV is somewhat subtle when FT-VII is expressed (Weninger *et al.*, 2000), the inflammation-dependent leukocyte recruitment is retained in the FT-VII(−/−) mice. However, it is extinguished in the FT-IV(−/−)/FT-VII(−/−) mice, indicating that FT-IV contributes to E-, P-, and L-selectin ligand generation (Homeister *et al.*, 2001).

Basophils represent <1% of the peripheral blood leukocytes. Under physiological conditions, basophils do not reside in the peripheral tissues. However, basophils can infiltrate into the skin during inflammatory conditions (Ito *et al.*, 2011). Despite the similarities of basophils and mast cells, recent studies have revealed unique functions for basophils, such as producing IL-4 and IL-13 (Redrup *et al.*, 1998; Sokol *et al.*, 2008; Watanabe *et al.*, 2008), and functioning as antigen-presenting cells that induce Th2 cells (Sokol *et al.*, 2009). Basophils also mediate protective immunity against helminthes and ticks (Voehringer, 2009; Wada *et al.*, 2010), in addition to being indispensable for IgG-mediated anaphylactic reactions in mice (Tsujimura *et al.*, 2008).

IgE-mediated chronic allergic inflammation (IgE-CAI) is a long-lasting inflammation that follows immediate-type reactions and late-phase responses. It is histopathologically characterized by numerous eosinophils and mast cells (Mukai *et al.*, 2005; Obata *et al.*, 2007). Although tissue basophils constitute only a minor population of total cellular infiltrate, they have a critical role in the development of IgE-CAI. After a depletion of basophils but not the mast cells, it has been

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*Abbreviations: CHS, contact hypersensitivity; FT, α(1, 3) fucosyltransferase; IgE-CAI, IgE-mediated chronic allergic inflammation; mRNA, messenger RNA; PSGL-1, P-selectin glycoprotein-1; TNP, trinitrophenyl; WT, wild type*

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shown that there is an almost complete abrogation of IgE-CAI (Obata *et al.*, 2007). Thus, basophils are now considered to initiate inflammation of IgE-CAI. Nevertheless, the current understanding of early events involving basophil recruitment to the skin remains limited. This study was designed to determine the requirements of selectin ligand activity for initial basophil recruitment to the skin controlled by FT-IV and -VII during IgE-CAI.

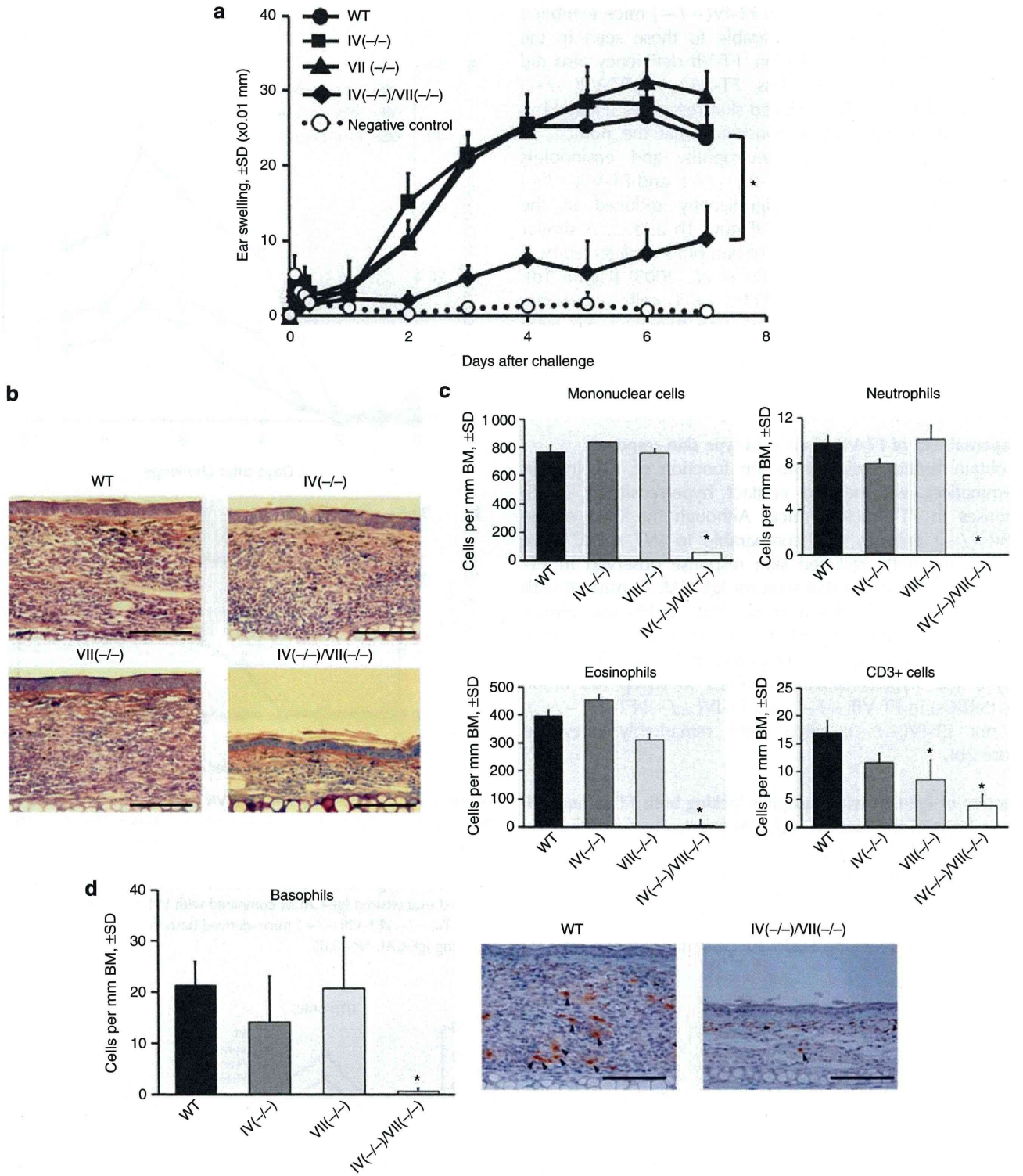


**Figure 1. IgE-mediated chronic allergic inflammation (IgE-CAI) in α(1, 3) fucosyltransferase-IV (FT-IV)- and/or FT-VII-deficient mice.** (**a**) IgE-CAI was induced in mice lacking FT-IV and/or FT-VII. Negative control mice were challenged with trinitrophenyl-OVA (TNP-OVA) without TNP-IgE injection. (**b**) Histopathological features of the skin (Giemsa's staining). (**c**) Cell populations in inflammatory skin. (**d**) Basophil numbers in inflammatory skin. Basophils were detected by mouse mast cell protease-8 mAb (arrows in the right panel). *$P<0.05$ compared with wild-type (WT) mice. BM, basement membrane. Bar = 100 μm.

## RESULTS

### Dependency of IgE-CAI on the collaborative functions of FT-IV and FT-VII

To determine selectins and FTs contribution to skin inflammation, IgE-CAI was induced in FT-IV(−/−), FT-VII(−/−), and FT-IV(−/−)/FT-VII(−/−) mice. FT-IV(−/−) mice exhibited levels of skin responses comparable to those seen in the wild-type (WT) mice. In addition, FT-VII deficiency also did not affect IgE-CAI. Nevertheless, FT-IV(−/−)/FT-VII(−/−) mice showed remarkably reduced skin responses (Figure 1a). Histological examination demonstrated that the number of dermal mononuclear cells, neutrophils, and eosinophils were similar among the WT, FT-IV(−/−), and FT-VII(−/−) mice, although they were significantly reduced in the FT-IV(−/−)/FT-VII(−/−) mice (Figure 1b and c). A similar trend was noted for the number of basophils as detected by a basophil-specific antibody (Ugajin *et al.*, 2009) (Figure 1d). Conversely, the number of CD3 (+) T cells apparently decreased in FT-VII(−/−) mice, with this decrease even more prominent in FT-IV(−/−)/FT-VII(−/−) mice (Figure 1c). These findings demonstrate that IgE-CAI is dependent on both FT-IV and FT-VII.

### Indispensability of FT-VII in delayed-type skin responses

To obtain further insight into the function of FTs in skin inflammation, we induced contact hypersensitivity (CHS) responses in FT-deficient mice. Although the CHS of the FT-IV(−/−) animals was comparable to WT mice, there was a significantly reduced skin response observed in FT-VII(−/−) mice, unlike that seen for IgE-CAI. Consistent with a previous report (Smithson *et al.*, 2001), CHS was almost completely absent in FT-IV(−/−)/FT-VII(−/−) mice (Figure 2a). Similarly, as compared with the WT mice, delayed-type hypersensitivity reactions to sheep red blood cells (SRBCs) in FT-VII(−/−) and FT-IV(−/−)/FT-VII(−/−), but not FT-IV(−/−), mice were remarkably alleviated (Figure 2b).

### Induction of IgE-CAI with basophils lacking both FT-IV and VII

On the basis of the fact that IgE-CAI is entirely dependent on basophils (Mukai *et al.*, 2005; Obata *et al.*, 2007), we attempted to determine the contribution of selectin ligands generated by basophil FTs to the development of skin responses. Basophil transfer from WT mice to irradiated FcRγ(−/−) mice lacking FcεRI successfully induced IgE-CAI (Figure 3a), which was consistent with a prior report (Mukai *et al.*, 2005). Basophil-enriched cell suspension consisted of ~20% primary basophils and ~80% other cells, including CD49b (+) natural killer (NK) cells. Nevertheless, NK cells, T cells, NKT cells, B cells, and

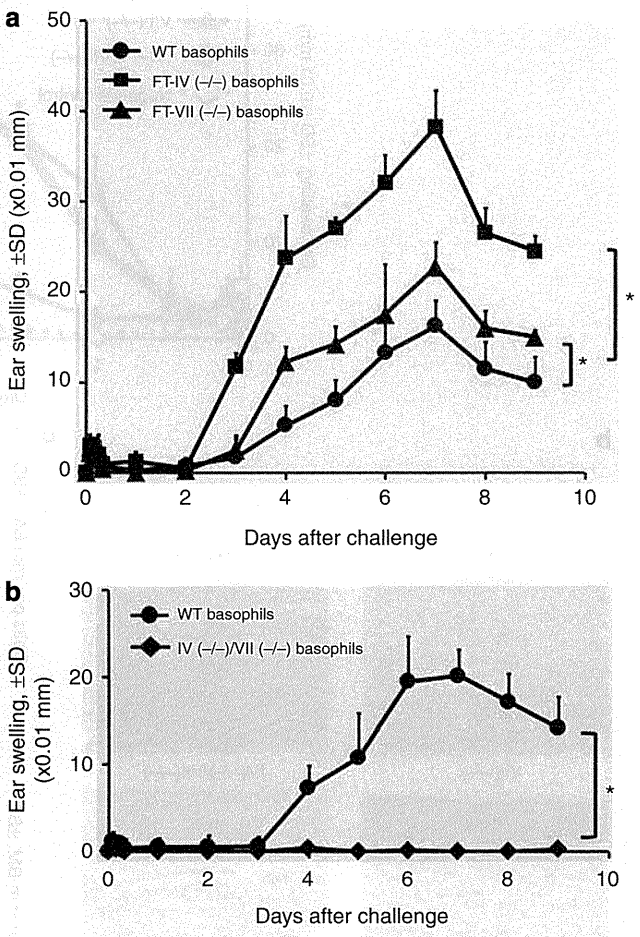


**Figure 3. α(1, 3) Fucosyltransferase-IV/VII (FT-IV/VII) in basophils are indispensable for IgE-mediated chronic allergic inflammation (IgE-CAI).** IgE-CAI was induced in FcRγ(−/−) mice that received primary basophils from wild-type (WT), FT-IV(−/−), FT-VII(−/−), and FT-IV(−/−)/FT-VII(−/−) mice. (**a**) Although basophils from FT-IV(−/−) and FT-VII(−/−) mice induced exacerbated IgE-CAI as compared with WT basophils, (**b**) FT-IV(−/−)/FT-VII(−/−) mice–derived basophils were incapable of inducing IgE-CAI. *$P<0.05$.

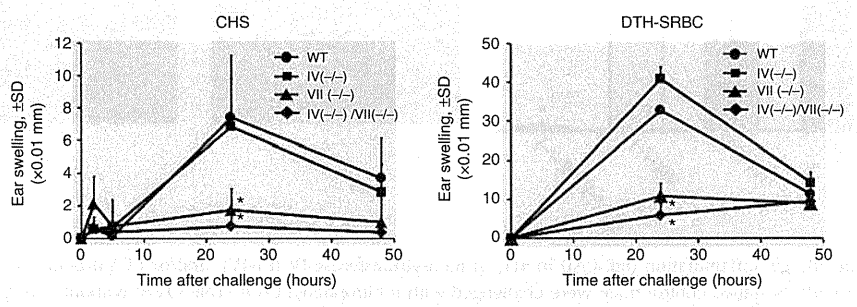


**Figure 2. Delayed-type hypersensitivity (DTH) reactions in α(1, 3) fucosyltransferase-IV (FT-IV)- and/or FT-VII-deficient mice.** Contact hypersensitivity (CHS) and DTH to sheep red blood cells (DTH-SRBCs) were induced in mice lacking FT-IV and/or -VII. *$P<0.05$ compared with wild-type (WT) mice.

dendritic cells are dispensable for IgE-CAI (Mukai *et al.*, 2005), and thus the development of IgE-CAI in FcRγ(−/−) mice in this experiment could be exclusively mediated by primary basophils. This was also confirmed by the results that IgE-CAI in mice receiving basophil-enriched cell suspension was remarkably alleviated when recipient mice were treated with basophil-depletion antibody (Ba103, kindly provided by Dr Karasuyama (Obata *et al.*, 2007)) (Supplementary Figure S1 online). Basophils from FT-VII(−/−) mice were also capable of inducing IgE-CAI, and interestingly there were higher induction levels as compared with those seen for the WT basophils. This exacerbation was even more marked when basophils were transferred from FT-IV(−/−) mice. Conversely, skin responses in FcRγ(−/−) mice that underwent transfers of primary basophils from FT-IV(−/−)/FT-VII(−/−) mice were completely absent (Figure 3b). Thus, IgE-CAI is entirely dependent on basophil selectin ligands that are collaboratively generated by FT-IV and FT-VII.

**Expression of functional selectin ligands on basophils is not sufficient for the full development of IgE-CAI**

As inflammatory cells, such as T cells, neutrophils, and eosinophils, have FT-IV and/or FT-VII and are recruited to the skin in a selectin-dependent manner (Homeister *et al.*, 2001; Smithson *et al.*, 2001; Satoh *et al.*, 2005), we examined the development of IgE-CAI by performing experiments designed to assess the contribution of selectin ligands generated by FT-IV/VII in cells other than basophils. WT basophils together with CD49b (−) bone marrow cells (effector cells) from either WT or FT-IV(−/−)/FT-VII(−/−) mice were transferred to irradiated FT-IV(−/−)/FT-VII(−/−) mice. Transfers with the CD49b (−) effector cells from WT mice resulted in a successful induction of IgE-CAI in FT-IV(−/−)/FT-VII(−/−) mice (Figure 4a). Although the CD49b (−) effector cells from FT-IV(−/−)/FT-VII(−/−) mice also induced IgE-CAI responses, induction levels were lower than those of the mice receiving WT mice–derived

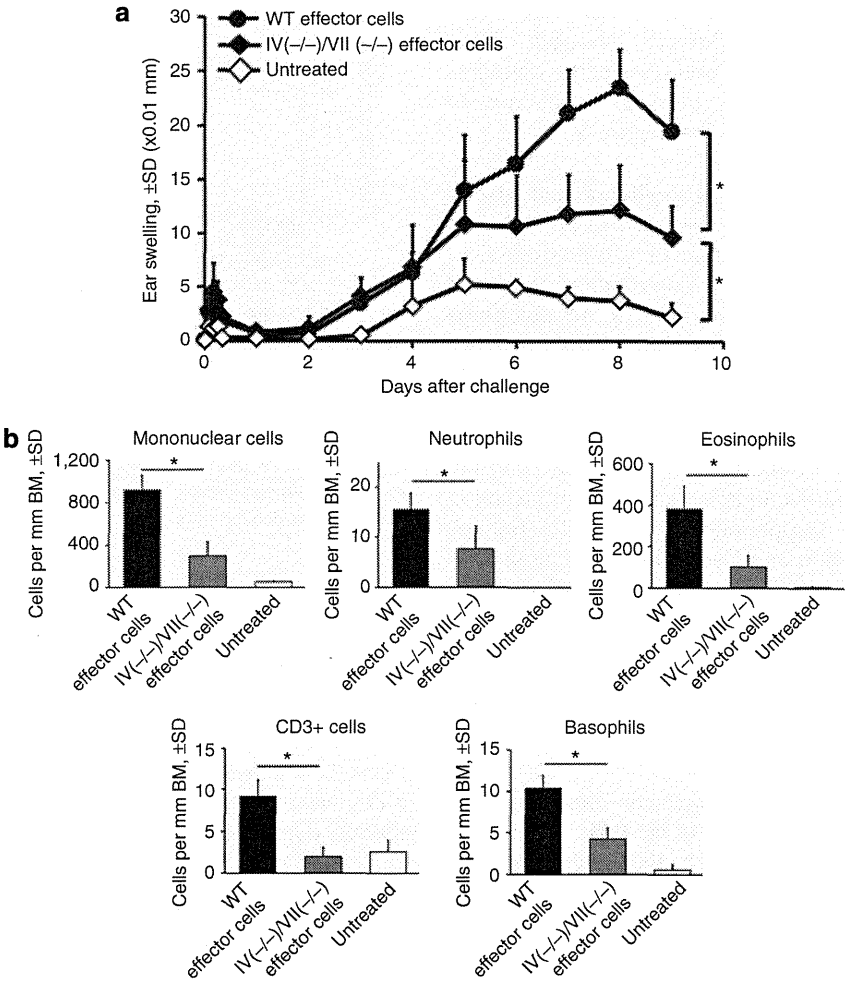


**Figure 4. Selectin-dependent cooperative recruitment of basophils and effector cells.** (**a**) Irradiated α(1, 3) fucosyltransferase-IV (FT-IV)(−/−)/FT-VII(−/−) mice received wild-type (WT) basophils in combination with CD49b(−) bone marrow cells (effector cells) from either WT or FT-IV(−/−)/FT-VII(−/−) mice. They were then immunized with trinitrophenyl-IgE (TNP-IgE) and challenged with TNP-OVA. The untreated group comprised FT-IV(−/−)/FT-VII(−/−) mice without cell transfer. (**b**) Cell populations in inflammatory skin. *$P<0.05$ compared with WT effector cells. BM, basement membrane.

CD49b (−) effector cells. When cell populations from inflammatory skin were analyzed, it was shown that, even in the presence of WT basophils, there was an impairment of the recruitment of mononuclear cells, neutrophils, CD3 (+) T cells, and eosinophils in mice transferred with FT-IV(−/−)/FT-VII(−/−) mice–derived CD49b(−) effector cells (Figure 4b). More importantly, when WT basophils were cotransferred with CD49b (−) effector cells from FT-IV (−/−)/FT-VII(−/−) mice, complete recruitment into the skin was not achieved. These data suggest that selectin-dependent recruitment of the effector cells appears to be necessary for sufficient responses of IgE-CAI and effective basophil infiltration to occur, even though functional selectin ligand generation in basophils by FT-IV/VII is essential for skin inflammation.

**Binding of E- and P-selectins to basophils *in vitro***

Primary basophils expressed transcripts of FT-IV and FT-VII messenger RNA (mRNA; Figure 5a). This was in contrast to bone marrow–derived mast cells, which only expressed extremely low levels of FT mRNA. Although bone marrow–derived basophils had FT transcripts, the levels were much lower than those seen for the primary basophils. Flow cytometry results showed that E- and P-selectin chimeras could bind to primary basophils from WT but not to FT-IV(−/−)/FT-VII(−/−) mice *in vitro* (Figure 5b).

**Blockade of E- and/or P-selectins and the amelioration of IgE-CAI**

Given the evidence that basophil expression of both E- and P-selectin ligands was dependent upon FT-IV/VII expression, we next attempted to determine the contribution of E- and P-selectins to the actual basophil recruitment. To determine this, we initially examined the effects of blocking Abs against selectins on the development of IgE-CAI. Unexpectedly, we found that blocking of either the E- (clone 10E9.6, BD Bioscience Pharmingen (San Jose, CA), 100 μg per mouse, intravenous ) or P- (clone RB40.34, BD Bioscience Pharmingen, 100 μg per mouse, intravenous) selectins did not result in amelioration of IgE-CAI (Supplementary Figure S2 online). Similarly, dual blocking of P- and E-selectins by coadministration of these two Abs also failed to suppress IgE-CAI. These results were in a striking contrast to prior reports demonstrating that the same antibody clones against P- and E-selectins clearly alleviated eotaxin-induced eosinophil accumulation (Satoh *et al.*, 2005) and cutaneous arthus reaction (Yanaba *et al.*, 2003).

**Role of P-selectin glycoprotein-1 and L-selectin interaction in basophil recruitment and development of IgE-CAI**

Leukocytes express L-selectin, which then interacts with inducible endothelial ligands and contributes to leukocyte rolling (Spertini *et al.*, 1991, 1992; Luscinskas *et al.*, 1994; Tu *et al.*, 1999). Counter-receptor activity of the L-selectin ligand on endothelial cells has been shown to be dependent on the modification by FT-IV and/or VII (Maly *et al.*, 1996; Tu *et al.*, 1999). However, the interaction of basophil L-selectin with ligands modified by endothelial FTs did not seem to be part of the essential pathway for the development of IgE-CAI, as

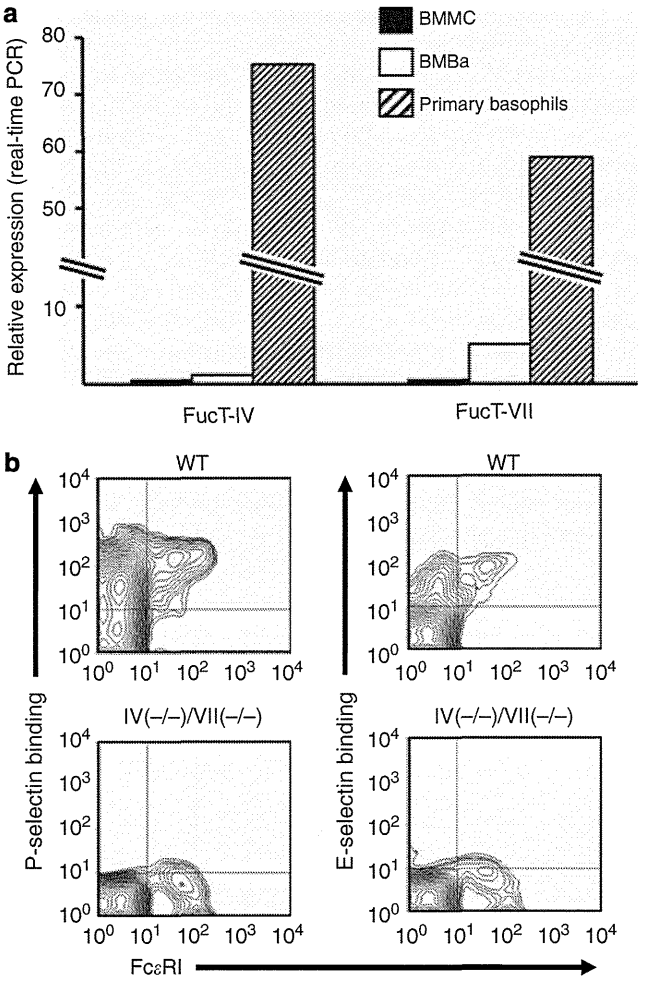


**Figure 5. Expression of α(1, 3) fucosyltransferase (FT) messenger RNA (mRNA) and FT-dependent selectin binding in basophils.** (**a**) Primary basophils were subjected to further purification by positive selection with CD123 (purity >99%). Transcripts for FT-IV and FT-VII mRNA were quantified by real-time PCR. (**b**) Binding of soluble P- and E-selectins to primary basophils assessed by flow cytometry. BMBa, bone marrow–derived basophil; BMMCs, bone marrow–derived mast cells.

basophils from WT mice were able to successfully induce skin inflammation in FT-IV(−/−)/ FT-VII(−/−) mice lacking counter-receptor activity for L-selectin on endothelial cells (Figure 4a). Prior evidence has also shown that leukocyte PGSL-1, which is a major ligand for P-selectin, can function as a counter-receptor for L-selectin in an FT-dependent manner, thereby contributing to secondary tethering(Guyer *et al.*, 1996; Walcheck *et al.*, 1996). These findings led us to hypothesize that modification of P-selectin glycoprotein-1 (PSGL-1) by FTs in basophils combined with the subsequent binding to L-selectin was an essential pathway for the development of IgE-CAI. To test this hypothesis, we initially confirmed that primary basophils from both WT and FT-IV(−/−)/FT-VII(−/−) mice expressed PSGL-1 and L-selectin on their cell surface (Figure 6a). PSGL-1 Ab (4RA10, BD Bioscience Pharmingen) almost completely inhibited the *in vitro* binding

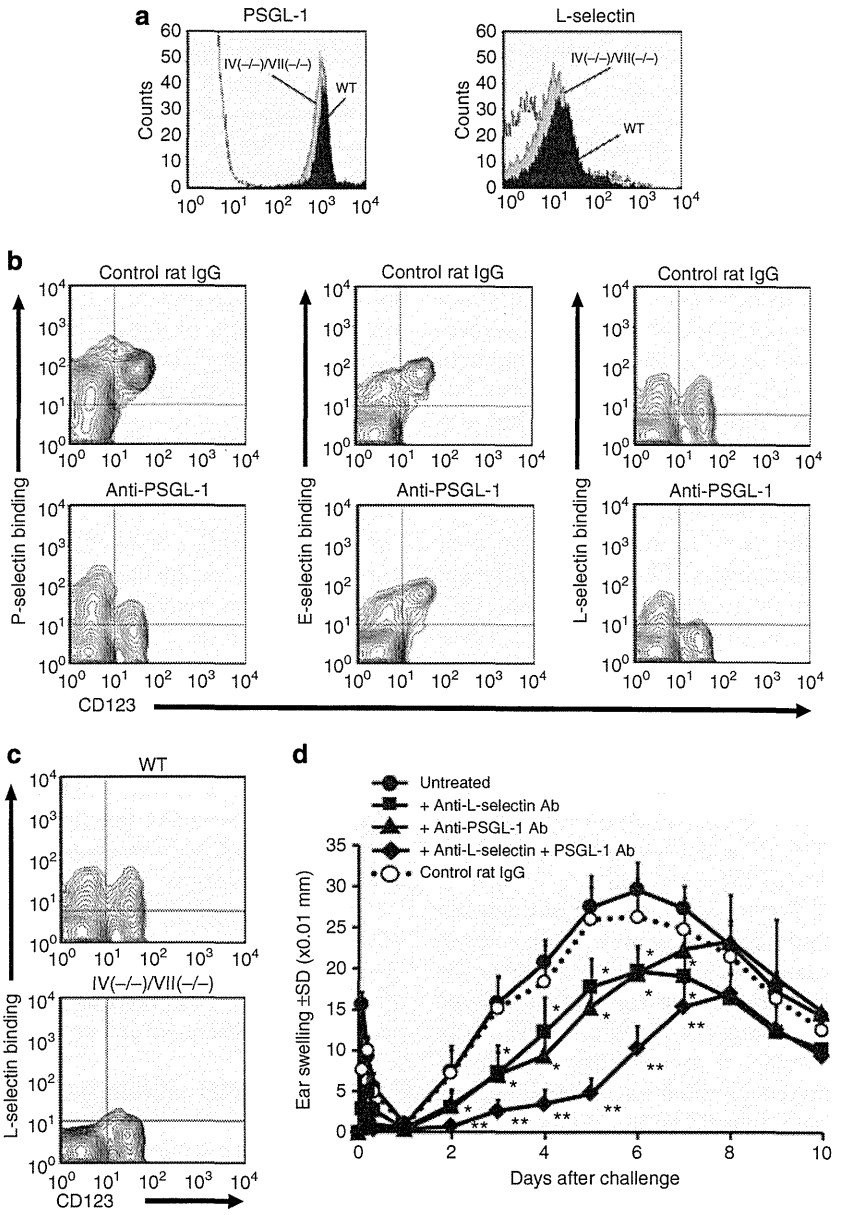


**Figure 6. Basophil P-selectin glycoprotein-1 (PSGL-1)–L-selectin interaction involvement in IgE-mediated chronic allergic inflammation (IgE-CAI).** (**a**) PSGL-1 and L-selectin expressions on basophils. (**b**) PSGL-1 Ab effect on selectin binding to primary basophils. (**c**) L-selectin binding to basophils from wild-type (WT) and α(1, 3) fucosyltransferase-IV (FT-IV)(−/−)/FT-VII(−/−) mice. (**d**) Effects of L-selectin and/or PSGL-1 Abs on IgE-CAI in WT mice. $*P<0.05$ compared with control IgG. $**P<0.05$ compared with L-selectin or PSGL-1 Ab alone.

of both the L- and P-selectins to the WT basophils (Figure 6b). Counter-receptor activity of PSGL-1 for L-selectin appears to be dependent on FT-VI/VII, as L-selectin failed to bind the primary basophils from FT-IV(−/−)/FT-VII(−/−) mice (Figure 6c). We then assessed whether blocking L-selectin could ameliorate IgE-CAI. As expected, the administration of the L-selectin blocking Ab (MEL-14, eBioscience, San Diego, CA) partly but significantly inhibited IgE-CAI. Similarly, PSGL-1 blocking Ab (4RA10) also inhibited IgE-CAI. When there was concomitant administration of these two Abs, further suppression of skin responses was also observed (Figure 6d).

## DISCUSSION

Extravasation and recruitment of basophils to the skin are an essential step for the development of IgE-CAI (Mukai *et al.*, 2005; Obata *et al.*, 2007). This study examined the FT-IV/VII-dependent basophil recruitment and induction of IgE-CAI.

Although a single deficiency of the *FT-IV* or *FT-VII* genes did not affect IgE-CAI, greatly impaired skin responses were seen in the FT-IV(−/−)/FT-VII(−/−) mice. To elucidate the contribution of FTs in basophils during IgE-CAI, we transferred basophils into FcRγ(−/−) mice lacking FcεRI. Unlike those from WT mice, basophils from the FT-IV(−/−)/FT-VII(−/−)

mice failed to induce IgE-CAI in FcRγ(−/−) mice. These data confirm the critical contribution of basophils for the development of IgE-CAI (Mukai *et al.*, 2005) and suggest that impaired skin responses in FT-IV(−/−)/FT-VII(−/−) mice is largely due to the inability to recruit basophils into the skin.

Leukocytes other than basophils may also require selectins for their recruitment to the skin during IgE-CAI. Our results indicated that the transfer of WT basophils with basophil-depleted bone marrow cells (effector cells) from FT-IV(−/−)/FT-VII(−/−) mice were not able to fully develop IgE-CAI as compared with the WT basophils that were cotransferred with WT effector cells (Figure 4a). In addition, WT basophils themselves were not effectively recruited into the skin when in the presence of effector cells from FT-IV(−/−)/FT-VI(−/−) mice. Thus, it appears that some effector cells require FT-IV/VII-dependent modification of selectin ligands in order to be recruited to the skin. In addition, these cells appeared to increase the effectiveness of basophil recruitment to the skin. Once basophils are recruited into the skin, they can promote the accumulation of other effector cells. These cells, in turn, may then assist in further basophil recruitment into the skin.

Basophils from FT-IV(−/−)/FT-VII(−/−) mice did not show avidity to soluble E- and P-selectins, which indicates that these are dependent on the FT function (Figure 5b). However, IgE-CAI was unexpectedly not suppressed after the use of blocking Abs against P- and E-selectins, despite the inability of basophils from FT-IV(−/−)/VII(−/−) mice to induce IgE-CAI (Figure 3b). Conversely, blockade of L-selectin resulted in a moderate suppression of IgE-CAI. It is possible that PSGL-1 on basophils could be a counter-receptor of the basophil L-selectin. On the basis of our results that showed that WT basophils could successfully induce IgE-CAI in FT-IV(−/−)/FT-VII(−/−) mice, it appears that endothelial L-selectin ligands might not be essential for basophil recruitment. We demonstrated that L-selectin bound PSGL-1 *in vitro*, and this binding was dependent on the basophil FT-IV/VII. In addition, when we blocked PSGL-1, this alleviated IgE-CAI *in vivo*. These were similar to the level of suppression that was seen when using anti-L-selectin Ab. Thus, FT-mediated modification of basophil PSGL-1 and the binding to L-selectin appear to be one of the important steps required for the development of IgE-CAI.

Intriguingly, we also noted that coadministration of anti-PSGL-1 and L-selectin Abs was able to more efficiently inhibit IgE-CAI than the injection of a single Ab. Although we have not been able to completely assure that optimal doses of each antibody were used, this suggests that an adhesion pathway other than PSGL-1-L-selectin interaction might contribute to the development of IgE-CAI. Several lines of evidence have suggested that an L-selectin-dependent leukocyte–leukocyte interaction facilitates the subsequent direct interaction of leukocytes with endothelial selectins, which leads to the amplification of initial leukocyte recruitment (Alon *et al.*, 1996; Walcheck *et al.*, 1996; Sperandio *et al.*, 2003). In this respect, endothelial L-selectin ligands and P-selectin might assist in the capture and rolling of basophils and effector cells on the endothelial cells following the PSGL-1-L-selectin interaction, although the blocking of P-selectin alone is not sufficient for the inhibition of basophil recruitment and the development of IgE-CAI. The roles of E-, P-, and L-selectins in leukocyte capture and/or rolling on endothelial cells have been shown to be partially redundant, and these three selectins can also function synergistically (Ley *et al.*, 1993, 1995; Ley and Tedder, 1995; Lowe, 2002).

IgE-CAI offers a unique mouse model of skin inflammation, in that it is dependent on IgE and FcεRI of basophils, but independent of FcεRI of mast cells and other cells that usually have central roles in some human allergic inflammations (von Bubnoff *et al.*, 2003). In addition, the characteristics of mouse basophils differ from those of human basophils in many respects (Lee and McGarry, 2007). Another difference between humans and mice is seen in the regulatory functions of FTs. Human FT-VII, but not FT-IV, modifies PSGL-1 of leukocytes, leading to the expression of cutaneous lymphocyte–associated antigen, which acts as a functional selectin ligand and skin-homing receptor (Kieffer *et al.*, 2001). On the other hand, murine leukocytes express barely detectable levels of cutaneous lymphocyte–associated antigen epitope despite the expression of FT-VII, but still efficiently bind to E- and P-selectins. Murine FT-VII appears to fucosylate only a few quite specific glycans that interact preferentially with selectins (Kobzdej *et al.*, 2002). Thus, it would be difficult to consider the present findings for IgE-CAI in mice as directly applicable to human allergic skin diseases.

Collectively, basophil recruitment and development of IgE-CAI are entirely dependent on collaborative control by FT-IV and VII in the basophils. L-selectin binding to basophil PSGL-1 modified by the FTs could be a central event that ultimately leads to the subsequent inflammatory steps of IgE-CAI.

## MATERIALS AND METHODS

### Mice

C57BL/6 mice were purchased from Sankyo Labo Service (Tokyo, Japan). FcRγ chain(−/−) C57BL/6 mice (Takai *et al.*, 1994) were kindly provided by Dr Takai of Tohoku University, Japan. FT-IV(−/−) mice, FT-VII(−/−) mice, and FT-IV(−/−)/FT-VII(−/−) mice (Maly *et al.*, 1996; Homeister *et al.*, 2001) were originally established at the University of Michigan (Dr Lowe), with colonies maintained at Case Western Reserve University (Dr Myers), which provided animals to our department. The use of animals was in full compliance with the Committee for Animal Experiments of Tokyo Medical and Dental University.

### Antibodies

Isotype-matched control Ab (rat IgG2aκ), rat anti-CD16/CD32 (2.4G2), biotinylated anti-CD49b (Dx5), and PE-labeled anti-PSGL-1 (P-selectin glycoprotein-1) (2PH1) Abs were from BD Bioscience Pharmingen. PE/Cy5-labeled anti-L-selectin Ab (MEL-14) was from BioLegend (San Diego, CA). FITC-conjugated anti-CD49b (Dx5), FITC- and PE-conjugated anti-FcεRI Ab (MAR-1), FITC- and PE-labeled anti-mouse CD123 (IL-3Rα), and PE-labeled anti-c-kit (ACK2), biotinylated anti-c-kit (2B8) Abs were purchased from eBioscience. Anti-CD3e (M-20) was from Santa Cruz Biotechnology