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221	戸倉新樹：	Chapter3 抗ヒスタミン薬の適応疾患 ８．接触皮膚炎.	ファーマナビゲーター 抗ヒスタミン薬編. メディカルレビュー社		130-137	2012	
222	戸倉新樹：	薬物治療と副作用の指針／光接触皮膚炎の診断・治療指針.	運動器診療最新ガイドライン. 総合医学社		74-75	2012	
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224	戸倉新樹：	４．皮膚リンパ腫の診断手順.	皮膚科臨床アセット１３　皮膚のリンパ腫最新分類に基づく診療ガイド. 中山書店		16-22	2012	
225	戸倉新樹（分担）：	ATL の皮疹型と診察への反映に関する研究.	厚生労働科学研究費補助金　がん臨床研究事業（H23-がん臨床-一般-022）平成23 年度総括・分担研究報告書		51-53	2012	
226	戸倉新樹，鬼頭由紀子：	好酸球性膿疱性毛包炎の病態解明と新病型分類の提言.	厚生労働科学研究費補助金（難治性疾患克服研究事業）好酸球性膿疱性毛包炎の病態解明と新病型分類の提言　平成23 年度総括・分担研究報告書		13-16	2012	
227	戸倉新樹，朴紀央，鬼頭由紀子：	痒疹病変部におけるサイトカインプロフィールの解析及び内因性アトピー性皮膚炎との関連に関する研究.	厚生労働科学研究費補助金（難治性疾患克服研究事業）難治性慢性痒疹・皮膚掻痒症の病態解析及び診断基準・治療指		54-58	2012	

			針の確率平成21年度～23年度総合研究報告書				
228	笛木修，戸倉新樹，小野寺博志，今井弘一，細井一弘，山田弘：	光毒性試験代替法の第三者評価報告書／評価対象：酵母光生育阻害試験と赤血球光溶血試験の組み合わせ.	AATEX-JaCVAM（日本動物実験代替法学会機関誌）J1		45-87	2012	
229	戸倉新樹：	浜松と北九州の皮膚病の違い.	泰玄会ニュース	XVI	7-8	2012	
230	戸倉新樹：	ＪＤ編集長に聞く.	JDA NEWS LETTER	13	9	2012	
231	戸倉新樹：	アレルギーと免疫の立場を再考する.	アレルギー・免疫	19	7	2012	
232	戸倉新樹：	肌を乾燥から守る[入浴」のポイント.	介護ビジョン	12	70-71	2012	
233	鬼頭由紀子、橋爪秀夫、戸倉新樹：	左眼瞼周囲の浮腫性硬化.	第11回浜名湖皮膚病理研究会記録集		26-27	2011	
234	笛木はるな、日野亮介、中島大毅、中村元信、戸倉新樹、島尻正平：	下腿の巨大腫瘤.	第11回浜名湖皮膚病理研究会記録集		29	2011	
235	戸倉新樹：	薬疹におけるリンパ球刺激試験（DIST）の意義.	診る・わかる・治す 皮膚科臨床アセット 2 薬疹診療のフロントライン. 中山書店		42-47	2011	
236	伊豆邦夫、森智子、戸倉新樹：	アトピー性皮膚炎に対するタクロリムス軟膏の使用経験—全身への外用療法による皮疹と QOL の改善--.	Progress in Medicine. ライフ・サイエンス	31	1573-1577	2011	
237	尾藤利憲、大森俊、吉澤真佑子、春山護人、澤田雄宇、川上	日光角化症と Bowen 病に対するメタルハライドランプを用いた光線力学両方	西日本皮膚科別冊	73	260-265	2011	

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238	大森俊、日野亮介、春山護人、尾藤利憲、中村元信、戸倉新樹：	Malignant nodular hidradenoma の 1 例.		65	422-426	2011	
239	池谷茂樹、浦野聖子、小出まさよ、戸倉新樹：	顕著な炎症を伴った汗孔角化症.	皮膚科診療	33	813-816	2011	
240	吉岡学、久保利江子、日野亮介、小林美和、中村元信、戸倉新樹：	全身に皮疹を認めた職業性クロムアレルギー.	皮膚病診療	33	1023-1026	2011	
241	戸倉新樹：	皮脂欠乏症湿疹とアトピー性皮膚炎.	J Visual Dermatol	10	1260-1261	2011	
242	戸倉新樹：	Dennie-Morgan folds を伴うアトピー性皮膚炎.	J Visual Dermatol	10	1288-1289	2011	
243	杉田和成、戸倉新樹：	魚アレルギーとアトピー性皮膚炎.	J Visual Dermatol	10	1302-1303	2011	
244	杉田和成、戸倉新樹：	angiohistiocytoid palules.	J Visual Dermatol	10	1306-1307	2011	
245	澤田雄宇、戸倉新樹：	アトピー性皮膚炎に伴った chondrodermatitis of the auricle.	J Visual Dermatol	10	1308-1309	2011	
246	杉田和成、戸倉新樹：	炎症性辺縁隆起性白斑.	J Visual Dermatol	10	1310-1311	2011	
247	池谷茂樹，浦野聖子，小出まさよ，戸倉新樹：	顕著な炎症を伴った汗孔角化症.	皮膚病診療	33	813-816	2011	
248	戸倉新樹，宮地良樹：	いま，接触皮膚炎は.	皮膚アレルギーコンパクトセミナー	6	4-7	2011	
249	戸倉新樹：	特集に寄せて.	アレルギーの臨床	31	196	2011	
250	戸倉新樹：	Th 17 細胞と薬疹.	アレルギーの臨床	31	495-499	2011	

251	戸倉新樹：	2 つのアトピー性皮膚炎：外因性と内因性.	皮膚アレルギーフロンティア. メディカルレビュー社	9	60-63	2011	
252	戸倉新樹：	二つのアトピー性皮膚炎.	日本香粧品学会誌	35	19-22	2011	
253	戸倉新樹：	コリン性蕁麻疹の病態理解の新展開.	アレルギーの臨床	31	37-41	2011	
254	戸倉新樹：	減汗性コリン性蕁麻疹の新見地.	J Environ Dermatol Cutan Allergol	5	85-90	2011	
255	澤田雄宇，尾藤利憲，戸倉新樹：	減汗性コリン性蕁麻疹の新知見.	日本皮膚アレルギー・接触皮膚炎学会雑誌	5	85-90	2011	
256	戸倉新樹：	皮膚疾患と Th17 リンパ球.	総合臨牀	60	1625-1626	2011	
257	戸倉新樹：	アトピー性皮膚炎の検査とその意味付け.	日本医師会雑誌	140	987-990	2011	
258	戸倉新樹：	瘙痒性皮膚疾患と睡眠障害.	薬局	62	44-48	2011	
259	戸倉新樹：	紫外線による免疫抑制と樹状細胞.	臨床免疫・アレルギー科	56	434-441	2011	
260	戸倉新樹：	palmar hyperlinearity と年齢.	J Visual Dermatol	10	1270-1271	2011	
261	坂部純一，戸倉新樹：	皮膚バリア機能を担うフィラグリンの成熟機構.	J Visual Dermatol	10	1272-1274	2011	
262	戸倉新樹：	内因性アトピー性皮膚炎をどう考えるか.	J Visual Dermatol	10	1292-1294	2011	
263	戸倉新樹：	炎症性辺縁隆起性白斑.	J Visual Dermatol	10	1310-1311	2011	
264	鬼頭由紀子，戸倉新樹，中島大毅：	アトピー性皮膚炎と好酸球性膿疱性毛包炎は合併するか.	J Visual Dermatol	10	1312-1313	2011	
265	坂部純一，黒田悦史，戸倉新樹：	PI3 キナーゼ経路による好塩基球におけるTh2サイトカインの産生制御.	臨床免疫・アレルギー科	56	622-627	2011	
266	戸倉新樹：	皮疹型は成人T細胞性白血病／リンパ腫の独立した予	血液内科	63	702-707	2011	

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268	織茂弘志, 戸倉新樹:	皮膚科用薬.	治療薬ハンドブック 2011. じほう		223-232	2011	
269	戸倉新樹:	類乾癬・菌状息肉症.	高齢者の皮膚トラブル FAQ. 診断と治療社		266-267	2011	
270	戸倉新樹:	アトピー性皮膚炎における獲得免疫の異常.	皮膚科臨床アセット.1. アトピー性皮膚炎. 中山書店		130-135	2011	
271	島内隆寿, 戸倉新樹:	皮疹を呈するその他のリンパ腫.	皮膚科サブスペシャリティーシリーズ 1冊でわかる皮膚がん. 文光堂		349-356	2011	
272	戸倉新樹:	熱傷.	皮膚疾患最新の治療 2011-2012. 南江堂		117	2011	
273	戸倉新樹:	アトピー性皮膚炎における獲得免疫の異常.	皮膚科臨床アセット1 アトピー性皮膚炎. 中山書店		130-135	2011	
274	戸倉新樹:	類乾癬・菌状息肉症.	高齢者の皮膚トラブル FAQ. 診断と治療社		266-267	2011	
275	織茂弘志, 戸倉新樹:	皮膚科用薬.	治療薬ハンドブック 2011. じほう		226-232	2011	

276	島内隆寿，戸倉新樹：	皮疹を呈するその他のリンパ腫.	1冊でわかる皮膚がん. 真興社		349-356	2011	
277	大森俊、戸倉新樹：	ムチン沈着性脱毛（リンパ腫）.	皮膚科フォトクリニックシリーズ 皮膚で見つける全身疾患～頭のてっぺんからつま先まで～. メディカルレビュー社		19	2011	
278	戸倉新樹：	蚊刺過敏症を示したリンパ増殖性疾患.	皮膚科診療カラーアトラス大系. 講談社		58	2011	
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280	戸倉新樹：	造血疾患のかゆみ—悪性リンパ腫のかゆみと治療.	臨床医必携−全身とかゆみ. 診断と治療社		124-126	2011	
281	清水宏、戸倉新樹（分担）、秋山真志、有田賢：	アトピー性皮膚炎の予防・治療法の開発及び確立に関する研究.	平成22年度総括･分担研究報告書			2011	
282	戸倉新樹（分担），朴紀央：	痒疹病変部におけるサイトカインプロフィールの解析に関する研究.	平成22年度総括･分担研究報告書		65-68	2011	
283	小笠原康悦、戸倉新樹（分担）、尾藤利憲、椛島利江子、森智子、杉田和成：	アトピー皮膚炎における外因性・内因性の2分別と金属アレルギーの関与に関する研究	厚生労働科学研究費補助金：平成22年度 総括研究報告書		51-64	2011	
284	宮地良樹、戸倉新樹（分担），中島大毅：	地域発症率からみた好酸球性膿疱性毛包炎における衛生環境仮説の検証.	厚生労働科学研究費補助金 平成		14-18	2011	

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285	清水宏、戸倉新樹（分担），秋山真志，有田賢：	アトピー性皮膚炎の予防・治療法の開発及び確立に関する研究．免疫アレルギー疾患等予防・治療研究事業	厚生労働科学研究費補助金　平成２２年度研究報告書（免疫アレルギー疾患分野）（第２分冊）		53-63	2011	
286	横積博雄，戸倉新樹，朴紀央：	痒疹病変部におけるサイトカインプロフィールの解析に関する研究．難治性慢性痒疹・皮膚瘙痒症の病態解析及び診断基準・治療指針の確率	厚生労働科学研究費補助金　難治性疾患克服研究事業　平成 22 年度位総括・分担研究報告書		65-68	2011	
287	戸倉新樹：	蚊アレルギー．	日本小児皮膚科学会雑誌	30	69	2011	
288	戸倉新樹：	皮膚科医が同じ皮膚科医と論じられない訳．	皮膚病診察	33	412	2011	
289	戸倉新樹：	記録集発行にあたって．	第 11 回浜名湖皮膚病理研究会記録集			2011	
290	戸倉新樹：	産業医科大学でのかけがえのない 8 年間と御礼．	赤煉瓦		9-10	2011	
291	戸倉新樹：	アレルギー・マーチ～皮膚科医からの意見～．	日本小児皮膚科学会雑誌	30	59	2011	
292	戸倉新樹：	アトピー性皮膚炎：表皮の時代．	Visual Dermatology	10	1251	2011	
293	産業医科大学進路指導部編集委員会（松本哲郎，戸倉新樹，中村早人，一瀬		産業医のためのギモン・難問相談室．診断と治療			2010	

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294	戸倉新樹（編集）:		ファーストステップ皮膚免疫学. 中外医学社			2010	
295	戸倉新樹：	編集企画にあたって. 遺伝子がかかわる皮膚疾患入門：責任遺伝子がはきりした疾患.	MB Derma	163		2010	
296	戸倉新樹：	「産業医のためのギモン•難問相談室」刊行にあたって.	産業医のためのギモン•難問相談室. 診断と治療社			2010	
297	戸倉新樹：	「三学会合同•皮膚アレルギー•環境職業皮膚科学国際会議」を終えて.	Topics in Atopy		47	2010	
298	一瀬豊日，中村早人，戸倉新樹：	本邦に必要とされる専属産業医数：事業所•企業統計調査（総務省統計局経済基本構造統計課）から推計.	産業医科大学雑誌	32	73-81	2010	
299	椛島利江子，尾藤利憲，田尻真貴子，川上千佳，深町晶子，吉木竜太郎，杉田和成，日野亮介，森智子，小林美和，中村元信，戸倉新樹：	塩酸オロパタジン内服によるアトピー性皮膚炎患者の血中サブスタンスPとTh17細胞割合への影響.	西日本皮膚科	72	159-161	2010	
300	小林美和，戸倉新樹，佐藤紀子，高木豊，北原隆，武馬吉則，河崎宏典：	月経に関連した外陰部皮膚症状に関するアトピー性皮膚炎患者へのアンケート調査.	西日本皮膚科	72	385-389	2010	
301	椛島利江子，尾藤利憲，日野亮介，中村元信，戸倉新樹：	ベシル酸ベポタスチン内服によるアトピー性皮膚炎患者の止痒効果とTh17細胞，Th2細胞の変動.	Progress in Medicine	30	2229-2232	2010	
302	小林美和，吉木竜太郎，坂部純一，中村元信，戸倉新樹：	ロキシスロマイシンの皮膚免疫調整作用.	皮膚の科学	9	17-20	2010	
303	杉田和成，椛島利江子，中村元信，戸倉	ミゾリビン内服が有効であった慢性苔癬状粃糠疹.	日本皮膚アレルギー•接	4	47-50	2010	

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304	深町晶子，川上千佳，戸倉新樹：	発症から 40 年以上経過した皮膚疣状結核.	皮膚病診療	32	259-262	2010	
305	椛島利江子，尾藤利憲，春山護人，椋本祥子，吉木竜太郎，中村元信，山本修，戸倉新樹：	上腕に商事，懸垂状外観を呈した巨大メルケル細胞癌.	Skin Cancer	25	38-41	2010	
306	田尻真貴子，永田貴久，山下淳二，三宅大我，戸倉新樹：	Birt-Hogg-Dubé 症候群.	西日本皮膚科	72	567-568	2010	
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IV. 研究成果の刊行物・別刷

Natural killer (NK)–dendritic cell interactions generate MHC class II-dressed NK cells that regulate CD4^{+} T cells

Masafumi Nakayama[a], Kazuyoshi Takeda[b], Mitsuko Kawano[a], Toshiyuki Takai[c], Naoto Ishii[d], and Kouetsu Ogasawara[a,1]

Departments of [a]Immunobiology and [c]Experimental Immunology, Institute of Development, Aging and Cancer, Tohoku University, Sendai 980-8575, Japan; [b]Department of Immunology, Juntendo University School of Medicine, Tokyo 113-8421, Japan; and [d]Department of Microbiology and Immunology, Tohoku University Graduate School of Medicine, Sendai 980-8575, Japan

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Natural killer (NK) cells contribute to not only innate but also to adaptive immunity by interacting with dendritic cells (DCs) and T cells. All activated human NK cells express HLA-DR and can initiate MHCII-dependent CD4^{+} T-cell proliferation; however, the expression of MHCII by mouse NK cells and its functional significance are controversial. In this study, we show that NK–DC interactions result in the emergence of MHCII-positive NK cells. Upon in vitro or in vivo activation, mouse conventional NK cells did not induce MHCII transcripts, but rapidly acquired MHCII protein from DCs. MHCII *H2-Ab1*–deficient NK cells turned I-A^{b}-positive when adoptively transferred into wild-type mice or when cultured with WT splenic DCs. NK acquisition of MHCII was mediated by intercellular membrane transfer called "trogocytosis," but not upon DAP10/12- and MHCI-binding NK cell receptor signaling. MHCII-dressed NK cells concurrently acquired costimulatory molecules such as CD80 and CD86 from DCs; however, their expression did not reach functional levels. Therefore, MHCII-dressed NK cells inhibited DC-induced CD4^{+} T-cell responses rather than activated CD4^{+} T cells by competitive antigen presentation. In a mouse model for delayed-type hypersensitivity, adoptive transfer of MHCII-dressed NK cells attenuated footpad swelling. These results suggest that MHCII-dressed NK cells generated through NK–DC interactions regulate T cell-mediated immune responses.

Natural killer (NK) cells have long been known to play important roles in innate immunity, but recently their contributions to adaptive immunity have also been reported (1). Following immunization or infection, NK cells migrate to draining lymphoid organs, where they interact with dendritic cells (DCs) and/or T cells (2). By production of cytokines such as IFN-γ and TNF-α and direct cell–cell contact, NK cells activate DCs to induce T-cell proliferation and differentiation (3, 4). However, NK cells can also negatively regulate adaptive immune responses (2, 5). For example, in mouse models of autoimmune diseases such as rheumatoid arthritis and experimental autoimmune encephalomyelitis, depletion of NK cells by anti-NK1.1 mAb exacerbates these diseases (5). However, the molecular mechanisms underlying negative immune regulation by NK cells are poorly understood (5). Although conventional mouse NK cells do not express MHCII, subpopulations of activated mouse NK cells have been found to express MHCII (6–9), suggesting that NK cells may directly regulate CD4^{+} T-cell responses. Of note, activated human NK cells express HLA-DR and can induce MHCII-dependent CD4^{+} T-cell proliferation (6, 10–13).

MHCII molecules are crucial for the presentation of peptides processed from extracellular proteins to CD4^{+} T cells, and they shape T-cell receptor repertoire development during T-cell maturation and lineage commitment. The constitutive expression of MHCII is restricted to professional antigen-presenting cells (APCs) such as DCs, macrophages, and B cells (14). In addition to professional APCs, basophils also express MHCII and play a crucial role as APCs (15). MHCII expression is transcriptionally regulated by the class II transactivator (CIITA) in APCs, including basophils (14, 15). However, the regulation of MHCII expression in murine NK cells and the mechanism by which MHCII^{+} NK cells are generated remain unclear.

A wide variety of immune cell lineages communicate with each other through direct cell–cell contact or cytokine production to establish appropriate immune responses. Several recent studies have shown that during direct cell–cell interactions, plasma membrane fragments of one cell are transferred to the opposite cell (16, 17). This phenomenon is currently called "trogocytosis" (17, 18), and it may generate novel cell populations that result from the interaction between two different types of immune cells. Indeed, Wakim and Bevan have recently reported that DC–DC interactions generate a novel DC subset, called "cross-dressed" DCs, which acquire peptide–MHCI complexes from donor DCs to drive memory CD8^{+} T-cell activation (19). Therefore, immune responses can be regulated not only by lineage-committed cell populations but also by cell populations generated independently of transcription, by trogocytosis. Whether NK–DC interactions produce novel cell populations in a similar manner has not been explored. Therefore, we investigated whether MHCII-positive NK cells could be generated through interactions between mouse conventional NK cells and splenic DCs, and asked whether the resulting MHCII-positive NK cells could regulate CD4^{+} T-cell responses.

Results

Activated NK Cells Express MHCII Protein, Although Not the Transcript, in Vivo. MHCII expression has been observed on human NK cells prepared from mixed lymphocyte cultures or pathogen-infected organs, suggesting that activated NK cells induce MHCII (10, 11). Consistent with these reports, we observed MHCII I-A^{b} expression on splenic NK1.1^{+} cells in C57BL/6 mice injected i.v. with the double-stranded RNA synthetic analog polyI:C, but not in naïve mice (Fig. 1*A*). These NK1.1^{+} cells also expressed NKG2D and DX5 (Fig. 1*A*), indicating that these cells were conventional NK cells. Expression levels of MHCII on splenic B cells and T cells were not altered by polyI:C administration (Fig. S1). To confirm that I-A^{b+} NK1.1^{+} cells were a single NK cell population and not merely conjugates of NK cells and I-A^{b+} cells such as DCs, we sort-purified these cells and analyzed them by

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[1]To whom correspondence should be addressed. E-mail: ogasawara@idac.tohoku.ac.jp.

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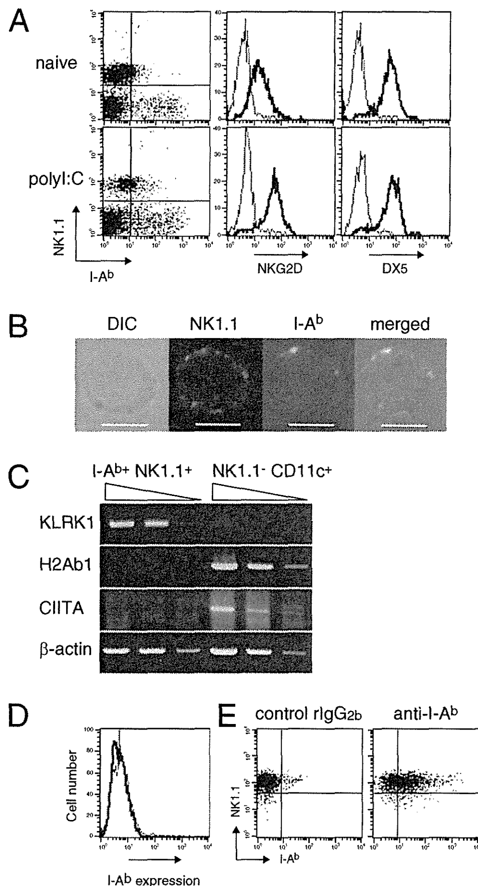

Fig. 1. Activated NK cells express MHCII protein but not the transcript in vivo. (*A*) NK1.1 and I-A^b expression on a non-T/B-cell population in spleen from naive or polyI:C (100 μg per mouse)-treated mice was analyzed (*Left*). Expression of NKG2D (*Center*) and DX5 (*Right*) on NK1.1$^+$ cells from splenocytes was analyzed using isotype control mAbs (thin lines) and specific mAbs (thick lines). (*B*) Purified I-Ab$^+$ DX5$^+$ cells were stained by AF488-anti–I-A^b mAb and biotinylated anti-NK1.1 mAb, followed by DyLight 594-streptavidin. (Scale bars, 5 μm.) (*C*) Expression of the indicated transcripts in purified splenic I-Ab$^+$ NK1.1$^+$ cells or NK1.1$^-$ CD11c$^+$ cells was analyzed by semiquantitative RT-PCR using 10-fold serially diluted cDNA templates. (*D*) Splenic NK cells were purified and then cultured with IL-2 (1,000 U/mL) for 5 d, and then stained with control rat IgG$_{2b}$ (thin line) or anti–I-A^b mAb (thick line). (*E*) NK cells cultured as described in *D* were labeled with CFSE and then transferred into mice. The following day, I-A^b and NK1.1 expression level on CFSE$^+$ cells in spleen was analyzed. Similar results were obtained in three (*A*, *D*, and *E*) or two (*B* and *C*) independent experiments.

confocal microscopy. Fig. 1*B* shows that NK1.1$^+$ cells per se express I-A^b on their cell surface.

To explore whether I-A^b expression on NK cells depended on transcriptional regulation, we next performed semiquantitative PCR on mRNA from sort-purified NK cells. Unexpectedly, we observed neither MHCII *H2-Ab1* transcript nor the transactivator *CIITA* transcript in I-A^{b+} NK1.1$^+$ cells, whereas we did detect the *Klrk1* gene transcript that encodes NKG2D protein in these cells (Fig. 1*C*). Thus, it appeared that the expression of MHCII protein on NK cells occurred independently of transcriptional regulation in vivo.

We next addressed whether activated NK cells express MHCII in vitro. We purified conventional NK cells from naïve mouse spleens and cultured them with IL-2 for 5 d. Unexpectedly, these conventional NK cells remained MHCII-negative in vitro (Fig. 1*D*). Interestingly, when we labeled the cells with 5- (and 6-) carboxyfluorescein diacetate succinimidyl ester (CFSE) and transferred them into naïve mice, these NK cells turned MHCII-positive in the spleens of recipient mice (Fig. 1*E*). Nevertheless, we were unable to detect *H2-Ab1* or *CIITA* transcripts in transferred I-A^{b+} NK cells purified from the spleens of recipient mice (Fig. S2). Thus, our findings suggest that activated NK cells become MHCII-positive in vivo, and do so by transcription-independent mechanisms.

Activated NK Cells Acquire MHCII from DCs Through NK–DC Interaction. To further elucidate the pathway for MHCII$^+$ NK cell generation, we next adoptively transferred IL-2-activated MHCII *H2-Ab1* gene-deficient NK cells into wild-type (WT) mice. Surprisingly, we found that MHCII was expressed at high levels on *H2-Ab1*–deficient NK cells in WT mouse spleens within 1 d of transfer (Fig. 2*A*). In contrast, WT NK cells transferred into *H2-Ab1*–deficient mice remained MHCII-negative (Fig. 2*A*). Given that activated NK cells interact with DCs in vivo (2), we hypothesized that NK cells acquire MHCII from DCs. To address this possibility, we cocultured CFSE-labeled NK cells and splenic DCs at a 1:1 ratio. We observed that IL-2-activated NK cells turned MHCII-positive within 1 h of coculture (Fig. 2*B*). In contrast, IL-

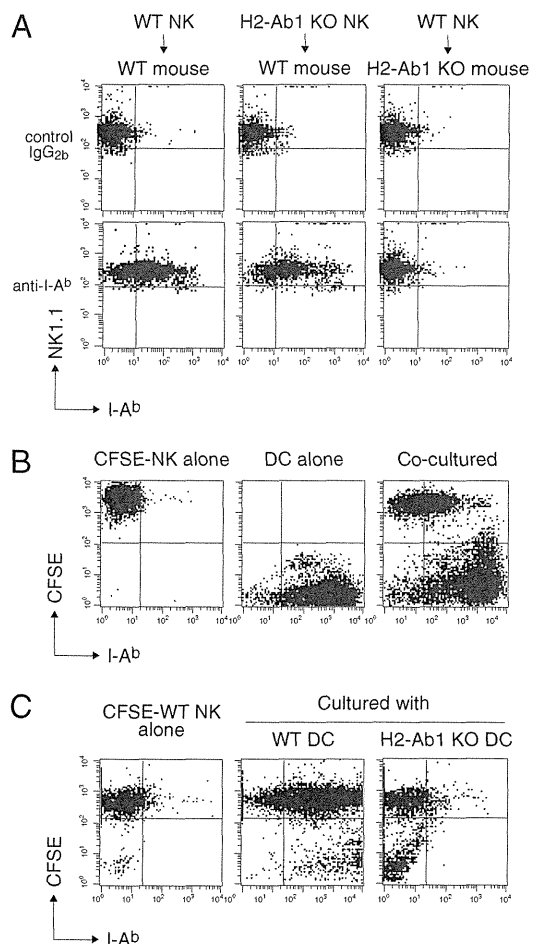

Fig. 2. Activated NK cells acquire MHCII from DCs. (*A*) WT or *H2-Ab1*–deficient NK cells prepared as described in Fig. 1*E* were adoptively transferred into WT or *H2-Ab1*–deficient mice. The following day, NK1.1 and I-A^b expression level on CFSE$^+$ cells in spleen was analyzed. (*B*) CFSE-labeled NK cells prepared as described in Fig. 1*D* were cocultured with splenic CD11c$^+$ cells at a 1:1 ratio for 1 h. I-A^b expression on these cells was analyzed. (*C*) CFSE-labeled WT NK cells were cocultured with WT or *H2-Ab1*–deficient splenic DCs, and I-A^b expression on these cells was analyzed as described in *B*. Similar results were obtained in three independent experiments.

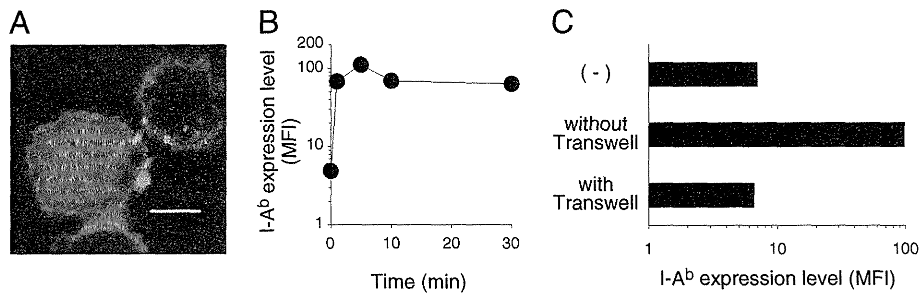

Fig. 3. Intercellular MHCII transfer is mediated by trogocytosis. (*A*) TAMRA-labeled NK cells cocultured with DCs were stained with AF488-anti–I-A^b mAb and analyzed by confocal microscopy. (Scale bar, 5 μm.) (*B*) CFSE-labeled NK cells were cocultured with DCs as described in Fig. 2*B* for the indicated periods of time. The mean fluorescence intensity (MFI) of I-A^b expression on NK cells was analyzed by flow cytometry. (*C*) CFSE-labeled NK cells were cocultured with DCs for 1 h together (no transwell) or separated by a semipermeable membrane (transwell). The MFI of I-A^b expression on NK cells was analyzed by flow cytometry. Similar results were obtained in three (*A* and *B*) and two (*C*) independent experiments.

2-activated WT NK cells remained MHCII-negative after coculture with *H2-Ab1*–deficient DCs (Fig. 2*C*), providing evidence that NK cells acquire MHCII from WT DCs. The acquired MHCII protein remained on NK cells for at least 12 h after removal of DCs (Fig. S3*A*). Freshly isolated splenic NK cells did not acquire MHCII protein from DCs effectively (Fig. S3*B*), and thus NK cells gain this ability once activated.

Intercellular protein transfer between immune cells is mediated by several pathways, including membrane nanotubes (transient long-distance connections), trogocytosis (a rapid, cell contact-dependent transfer of membrane fragment), and exosomes (secreted membrane nanovesicles of $\leq$100 nm) (16–18, 20). By confocal microscopy, we could not observe nanotubes between NK cells and DCs, but we found I-A^b-containing membrane fragments (~1 μm) from DCs on NK cells (Fig. 3*A*). Although DCs have been reported to secrete MHCII-containing exosomes (20), we did not detect exosomes in culture supernatants until 12 h after incubation (Fig. S4). In contrast, MHCII-containing membrane fragment transfer occurred within minutes (Fig. 3*B*). Furthermore, MHCII acquisition was completely abrogated by culturing NK cells and DCs in transwell plates (Fig. 3*C*), indicating that acquisition was dependent upon cell–cell contact. These results are consistent with the transfer of MHCII being mediated through trogocytosis rather than exosome secretion.

Trogocytosis is generally thought to be triggered by receptor signaling, and it has been reported that NK cells acquire MHCI and MHCI-related chain B from target cells by using NK cell receptors (NKRs) (21–23). Therefore, we conducted further studies to determine whether NKR signaling is required for MHCII acquisition. However, DAP10/12-deficient NK cells as well as WT NK cells acquired MHCII from DCs (Fig. S5*A*). WT NK cells also acquired MHCII from *β2-microglobulin*–deficient DCs that lacked cell surface expression of MHCI, indicating that MHCI-binding NKRs are not involved in this process (Fig. S5*A*). Consistent with these results, MHCII acquisition was not inhibited by an inhibitor of Syk family kinase, PI3K, or Src kinase (Fig. S5*B*). Neither did we observe the involvement of NK effector molecules such as perforin, IFN-γ, FasL, or TRAIL (24) in this process (Fig. S5). Interestingly, pretreatment of NK cells or DCs with cytochalasin D, an inhibitor of actin polymerization, or sodium azide, which depletes intracellular ATP, substantially inhibited MHCII transfer (Fig. S5*B*). Fixation of either NK cells or DCs with paraformaldehyde completely inhibited MHCII transfer (Fig. S5*B*). Collectively, these results suggest that activated NK cells acquire MHCII-containing DC membranes through a process that is dependent on plasma membrane and actin cytoskeleton interactions, but not NKR signaling or NK effector molecules.

MHCII-Dressed NK Cells Negatively Regulate CD4$^+$ T-Cell Proliferation. To explore whether MHCII-dressed NK cells could act as APCs to stimulate naïve T cells, we examined whether NK cells could also acquire costimulatory molecules from DCs by an in vitro coculture assay. Activated NK cells acquired CD80 and CD86, but the levels of these molecules on NK cells were minimal (Fig. S6).

We next examined whether MHCII-dressed NK cells could influence CD4$^+$ T-cell responses. We performed an antigen-presentation study using OT-II CD4$^+$ T cells specific for OVA$_{323–339}$/I-A^b. After coculture with WT or *H2-Ab1*–deficient

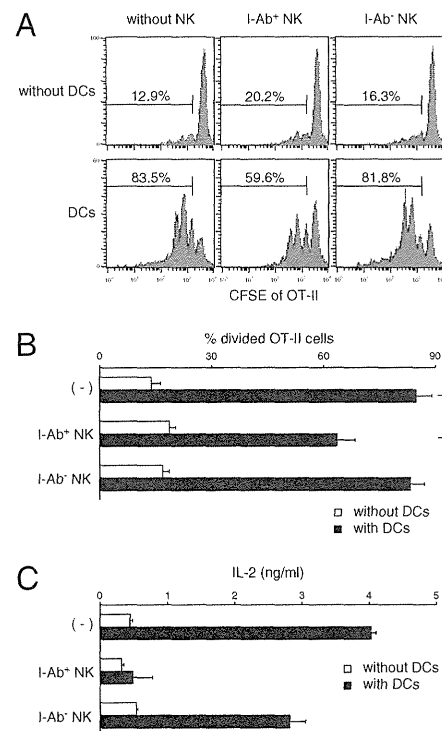

Fig. 4. MHCII$^+$ NK cells suppress CD4$^+$ T-cell proliferation induced by DCs. (*A*) NK cells were purified by cell sorting after coculture with WT DCs (I-A^{b+} NK) or *H2-Ab1*–deficient DCs (I-A^{b-} NK). CFSE-labeled OT-II CD4$^+$ T cells were cocultured with purified NK cells at a 1:10 ratio (NK:T), DCs at a 1:10 ratio (DC:T), or NK cells and DCs at a 1:1:10 ratio (NK:DC:T) in the presence of OVA$_{323–329}$ peptides (10 ng/mL) for 3 d. The CFSE intensity of OT-II CD4$^+$ cells was then analyzed. The percentages of divided OT-II cells are shown as means ± SD of triplicates in *B* (**P < 0.01 compared with DCs alone). (*C*) Production of IL-2 in the culture supernatants at 48 h after coculture was measured by ELISA. Similar results were obtained in three independent experiments.

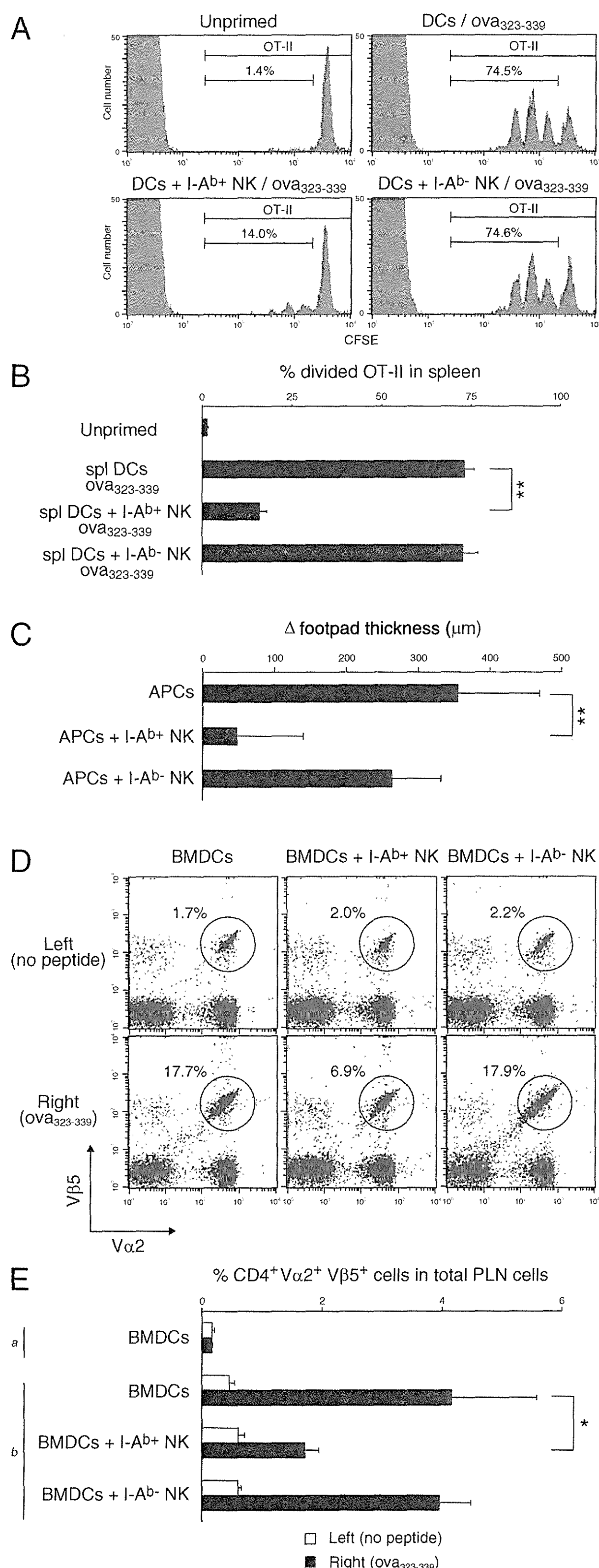

Fig. 5. MHCII$^+$ NK cells suppress CD4$^+$ T-cell responses in vivo. (*A*) B6 mice ($n = 3$) adoptively transferred with CFSE-labeled OT-II CD4$^+$ T cells were i.v. injected with OVA$_{323-339}$-loaded DCs or a mixture of these DCs and NK cells precultured with DCs together (I-A^{b+} NK cells) or separated (I-A^{b-} NK cells) as described in Fig. 3*C*. Two days later, CFSE intensity of CD4$^+$ Vα2$^+$ OT-II cells in spleen was analyzed. The percentage of divided OT-II cells is shown in *B*. B6 mice [$n = 4$ (*C*) or $n = 3$ (*D* and *E*)] adoptively transferred with activated OT-II CD4$^+$ T cells were s.c. injected with OVA$_{323-339}$-loaded APCs or a mixture of these APCs and I-A^{b+} NK or I-A^{b-} NK cells into the right footpads. The left footpads were injected with the same cell population without OVA$_{323-339}$ as controls. The following day, Δfootpad thickness was calculated by subtracting the left hind footpad thickness from the right (*C*). Three days after the s.c. injection, the percentage of Vα2$^+$ Vβ5$^+$ cells in total CD4$^+$ T cells in PLNs was analyzed (*D*) and the percentage of CD4$^+$ Vα2$^+$ Vβ5$^+$ cells in total PLN cells is calculated in *E*. (*a*) Naive mice. (*b*) OT-II CD4$^+$ T-cell transferred mice. *$P < 0.05$, **$P < 0.01$ compared with APCs alone. Similar results were obtained in two (*A* and *B*) or three (*C* and *D*) independent experiments. BMDCs, bone marrow-derived DCs.

DCs, I-A^b-dressed (I-A^{b+}) or I-A^b-negative (I-A^{b-}) NK cells were sort-purified. Purified I-A^{b+} NK cells did not induce naïve OT-II CD4$^+$ T-cell proliferation (Fig. 4 *A* and *B*), possibly due to insufficient expression of costimulatory molecules (Fig. S6). Interestingly, purified I-A^{b+} NK cells suppressed OT-II CD4$^+$ T-cell proliferation induced by DCs, whereas I-A^{b-} NK cells cocultured with *H2-Ab1*–deficient DCs did not (Fig. 4 *A* and *B*). Moreover, I-A^{b+} NK cells suppressed IL-2 production from OT-II CD4$^+$ T cells more effectively than I-A^{b-} NK cells (Fig. 4*C*). These results indicate that MHCII-dressed NK cells regulate CD4$^+$ T-cell responses to DCs via antigen presentation on MHCII without sufficient costimulation.

Furthermore, we addressed whether I-A^{b+} NK cells could suppress CD4$^+$ T-cell responses in vivo. Interestingly, I-A^{b+} NK cells significantly suppressed OT-II CD4$^+$ T-cell proliferation induced by DCs loaded with OVA$_{323-339}$ peptides in spleen, although I-A^{b-} NK cells did not affect the proliferation (Fig. 5 *A* and *B*). In a mouse model for delayed-type hypersensitivity (DTH) where activated OT-II CD4$^+$ T cells were i.v. transferred followed by s.c. injection with OVA$_{323-339}$-loaded APCs, I-A^{b+} NK cells attenuated footpad swelling (Fig. 5*C*) and reduced OT-II CD4$^+$ T-cell accumulation in the draining popliteal lymph nodes (PLNs) (Fig. 5 *D* and *E*). Taken together, these results suggest that MHCII-dressed NK cells suppress CD4$^+$ T-cell responses in vivo.

Discussion

In this study, we provide evidence that conventional murine NK cells do not transcriptionally induce MHCII but instead rapidly acquire MHCII protein from DCs through NK–DC interactions. These MHCII-dressed NK cells suppress CD4$^+$ T-cell responses to DCs by presenting antigen–MHCII complexes without sufficient costimulation, which might induce anergy in CD4$^+$ T cells. In addition, adoptive transfer of MHCII-dressed NK cells attenuated dermal DTH. Therefore, our findings may provide a mechanistic explanation for the negative immune regulation of T-cell immunity by NK cells.

Several recent studies have identified NK/DC hybrid-phenotype cells, which have functional properties characteristic of both NK cells and DCs (11, 25–28). IFN-producing killer DCs (IKDCs), also called B220$^+$ NK1.1$^+$ DCs, were identified as a novel DC subset harboring killer activity (27, 28). On the contrary, more recent studies have proposed that these killer DCs are functionally and developmentally activated NK cells (7–9). It remains unclear whether the MHCII-dressed NK cells we describe here are identical to the NK/DC hybrid-phenotype cells described in previous studies (25–28), although at least IKDCs and MHCII-dressed NK cells have similar antigenic phenotypes: CD11c$^+$ B220$^+$ MHCII$^+$ NKG2D$^+$ CD86^{dull+} Gr1$^-$ (Fig. S7). Interestingly, in a mouse model of type 1 diabetes, CD11c$^+$ DX5$^+$ cells, which are functionally and phenotypically similar to MHCII-dressed NK cells, were found to negatively regulate pathogenic T-cell activation (25). Of note, we observed that a small population of DCs cocultured with IL-2-activated NK cells became Ly49G2-positive (Fig. S8), suggesting that DCs

could also acquire NK cell surface proteins. Although this observation might also account for the generation of NK/DC hybrid-phenotype cells described in previous studies (25, 26), further studies will be necessary to characterize these hybrid-phenotype cells.

In addition, we observed that activated murine NK cells acquired MHCII from B cells in coculture experiments. However, the acquisition level of MHCII on these NK cells was lower than that on NK cells cocultured with DCs (Fig. S9), suggesting that activated NK cells preferentially acquired MHCII from DCs.

In contrast to mouse NK cells, after activation, all human NK cells synthesize HLA-DR as well as costimulatory molecules including CD80, CD86, and OX40 ligand (6, 11, 12). Unlike in humans, activation of mouse NK cells apparently does not induce the endogenous expression of MHCII.

Given that many cell types store a large excess of membrane on their cell surface (16), intercellular membrane transfer might occur frequently during immune cell–cell interactions. Recently, DCs have been reported to acquire peptide–MHCI complexes from distinct donor DCs and subsequently drive memory $CD8^+$ T-cell activation (19). T cells have also been reported to acquire CD80 and CD86 proteins from DCs by CTLA-4, thereby downmodulating the delivery of costimulatory signals (29). Our findings show that activated NK cells can acquire MHCII from DCs and regulate T-cell immune responses in vitro and in vivo. Taken together, it is possible that immune cells acquire additional functions and/or alter their intrinsic functions through intercellular transfer of immune regulatory molecules such as MHCII in lymphoid organs. Such newly generated cell populations could play important roles in the regulation of immune responses through their effects on other cell types.

Materials and Methods

Further details are available in *SI Materials and Methods*.

Mice. C57BL/6 mice were obtained from CLEA Japan. MHCII *H2-Ab1*–deficient mice (30) were kindly provided by D. Mathis (Harvard Medical School, Boston, MA). OT-II transgenic/rag-1 knockout mice were obtained from Taconic. These mice were maintained under specific pathogen-free conditions, and used according to the guidelines of the Institutional Animal Care and Use Committee established at Tohoku University.

RT-PCR. Total RNA was purified from cells using Sepasol (Nacalai). Complementary DNAs were synthesized from total RNAs by using oligo(dT) primer (Invitrogen). PCR was performed by using 10-fold serially diluted cDNA templates, AmpliTaq poly (Applied Biosystems), and primers listed in *SI Materials and Methods*.

NK–DC Interaction. Mouse splenic NK cells and DCs were prepared as described previously (31, 32). CFSE (0.5 μM)-labeled IL-2 (1,000 U/mL)-activated NK cells (5×10^5 per well) and splenic DCs (5×10^5 per well) were cocultured in a 96-well flat-bottom plate for the indicated periods at 37 °C. Then cells were stained with APC-labeled anti–I-A^b mAb (BioLegend) and analyzed on a FACSCanto II (BD Biosciences).

Confocal Microscopy. Cells were stained with 5- (and 6-) carboxytetramethylrhodamine succinimidyl ester (TAMRA; Invitrogen) or the following mAbs: AF488-anti–I-A^b, biotinylated anti-NK1.1 mAbs, and streptavidin-DyLight 594 (BioLegend). Then these cells were analyzed on a Carl Zeiss LSM510 confocal laser-scanning microscope equipped with a 63× objective lens as described previously (33).

In Vitro Antigen Presentation Assay. The antigen presentation assay was performed as described previously (32) with some modifications. Bone marrow-derived DCs (5×10^3 per well) and/or sort-purified NK cells (5×10^3 per well) were cocultured with CFSE (10 μM)-labeled OT-II $CD4^+$ T cells (5×10^4 per well) in a 96-well U-bottom plate for 3 d in the presence of $OVA_{323-339}$ peptides (10 ng/mL; Abgent). CFSE fluorescence intensity of OT-II $CD4^+$ T cells was analyzed by flow cytometry. Production of IL-2 in the culture supernatant at 48 h postaddition of OT-II $CD4^+$ T cells was measured by ELISA (eBioscience).

In Vivo OT-II Proliferation Assay. CFSE-labeled OT-II $CD4^+$ T cells (3×10^6 per mouse) were adoptively transferred into B6 mice. The following day, mice were i.v. injected with $OVA_{323-339}$ (1 μg/mL)-loaded splenic DCs (3×10^6 per mouse) or a mixture of these DCs (3×10^6 per mouse) and NK cells (3×10^6 per mouse). Two days later, mice were killed, and CFSE dilution of $CD4^+$ $V\alpha2^+$ splenocytes was analyzed by flow cytometry.

Dermal DTH. B6 mice adoptively transferred with activated OT-II $CD4^+$ T cells (6×10^6 per mouse) were s.c. injected with 50 μL of $OVA_{323-339}$-loaded APCs (2×10^7 per mouse) or a mixture of these APCs (2×10^7 per mouse) and NK cells (1×10^7 per mouse) into the right footpad. The left footpads were injected with the same cell population without $OVA_{323-339}$ as controls. Footpad thickness and infiltration of OT-II cells into PLNs were analyzed.

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