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Gene Expression Changes in Peripheral Blood Mononuclear Cells during Measles Virus Infection▽‡

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Measles virus continues to cause morbidity and mortality despite the existence of a safe and efficacious vaccine. Measles is associated with induction of both a long-lived protective immune response and immunosuppression. To gain insight into immunological changes during measles virus infection, we examined gene expression in blood mononuclear cells from children with acute measles and children in the convalescent phase compared to uninfected control children. There were 13 significantly upregulated and 206 downregulated genes. Upregulated genes included the immune regulatory molecules interleukin 1β (IL-1β), CIAS-1, tumor necrosis factor alpha, PDE4B, PTGS2, IL-8, CXCL2, CCL4, ICAM-1, CD83, GOS-2, IER3 (IEX-1), and TNFAIP3 (A20). Plasma levels of IL-1β and IL-8 were elevated during measles virus infection. Downregulated genes mainly involved three gene ontology biological processes, transcription, signal transduction, and the immune response, and included IL-16 and cell surface receptors IL-4R, IL-6R, IL-7R, IL-27RA, CCR2, and CCR7. Most mRNAs had not returned to control values 1 month after discharge, consistent with prolonged immune response abnormalities during measles virus infection.

Measles virus (MV) is remarkable for the robust immune response it elicits in the face of a generalized immune suppression that lasts several weeks following acute infection (10). After infection of the respiratory epithelium, MV is transported to the regional lymph nodes, probably by dendritic cells or macrophages (9). After replication in lymphoid tissue, there is systemic spread to multiple organs including skin, spleen, and liver. Infection induces a robust immune response beginning at the time of the rash with production of immunoglobulin M antibody to the MV nucleoprotein and induction of cellular immune responses. Antibodies are made to most MV proteins, with immunoglobulin G1 as the predominant isotype (9). The cellular immune response is responsible for the characteristic measles rash and is important for viral clearance (33, 48). Patients with agammaglobulinemia develop a rash and recover, while those with defects in cellular immunity may not (8, 23).

During the rash and recovery, there is evidence of immune activation that includes lymphoproliferation, an increase in plasma levels of soluble CD4 (sCD4), sCD8, soluble interleukin 2 receptor (IL-2R), β2-microglobulin, neopterin, sFas, sFasL, and soluble tumor necrosis factor receptor, and increased surface expression of Fas, CD25, and CD38 on circulating lymphocytes (10, 11, 37). Cytokines are also increased in plasma during the immune response to MV. Gamma interferon (IFN-γ) is detected early and then returns to baseline after the rash appears (26, 29). IL-2, IL-4, IL-10, and IL-13 are elevated during acute infection, and increased levels of IL-4 and IL-10 persist for several weeks after recovery (26). IL-12 levels are lower than those of the controls, indicating that some cytokine responses are downregulated by MV infection (1, 26, 29, 34). During acute disease and recovery, lymphoproliferative responses to mitogens and delayed type hypersensitivity responses to recall antigens are repressed, and there is an increased susceptibility to other infections (9, 13).

To better characterize MV-induced immunological changes at a transcriptional level, microarrays were used to globally survey mRNA levels in peripheral blood mononuclear cells (PBMCs) during acute measles and convalescence.

MATERIALS AND METHODS

Subjects and samples. Peripheral blood samples for microarray and plasma analysis were collected at a single time from three control children and at study entry, hospital discharge, and 1-month follow-up from five children hospitalized with measles at the University Teaching Hospital in Lusaka, Zambia (Table 1). The median numbers of days after rash onset at entry, discharge, and follow-up were 4, 8, and 40, respectively. Children with available PBMCs with high-quality RNA from all three time points were selected for microarray analysis from a larger prospective study of measles (24). Plasma samples from an additional 8 control children and 19 children with measles were used for analysis of plasma levels of cytokines and chemokines. All were confirmed to have measles and to be negative for human immunodeficiency virus type 1 (HIV-1) infection (24).

White blood cell (WBC) and differential counts were performed manually. Percentages of $CD4^+$ and $CD8^+$ lymphocytes were determined by flow cytometry as previously described (37). Plasma was separated and stored at −80°C. PBMCs were isolated on Ficoll-Hypaque gradients, washed, and stored in RNAzol or RNA-Stat (Tel-Test, Inc., Friendswood, TX) at −80°C. All studies were performed with protocols approved by the Committee for Human Research of the Johns Hopkins Bloomberg School of Public Health and the Ethics Committee of the University of Zambia.

GeneChip assays. RNAs from PBMCs of five children with measles and three control children (Table 1) were isolated following the manufacturer's instructions and used for microarray studies. RNA quality was determined by RNA Nano LabChip analysis on an Agilent Bioanalyzer 2100 (Agilent, Palo Alto, CA). For each sample, 100 ng of total RNA was processed according to the amplifi-

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TABLE 1. Clinical characteristics of patients and controls

Subject	Type	Age (mo)	Sex	No. of days after onset of rash at[a]:		
				Entry	Discharge	Follow-up
187	Control	26	Female	NA	NA	NA
188	Control	15	Male	NA	NA	NA
194	Control	9	Male	NA	NA	NA
33	Patient	21	Male	3	8	61
41	Patient	79	Female	2	4	36
43	Patient	9	Male	7	11	41
538	Patient	11	Female	4	9	39
536	Patient	8	Male	4	6	40

[a] NA, not applicable.

cation protocol from the Affymetrix GeneChip Eukaryotic Small Sample Target Labeling Technical Note, version 1 (Affymetrix, Santa Clara, CA). Two cycles of amplification, each with a cDNA synthesis step followed by an in vitro transcription reaction, were used to generate cRNA. The second in vitro transcription synthesis incorporated biotinylated ribonucleotides to produce labeled antisense cRNA targets for hybridization. Fifteen micrograms of cRNA was fragmented by metal-induced hydrolysis in fragmentation buffer (250 mM Tris acetate, pH 8.1, 150 mM magnesium acetate, 500 mM potassium acetate) at 94°C for 35 min. Hybridization cocktails were prepared as recommended for arrays of "Standard" format and applied to Affymetrix Human Genome U133A GeneChips. Hybridization was performed at 45°C for 16 h at 60 rpm in the Affymetrix rotisserie hybridization oven. The signal amplification protocol for washing and staining of eukaryotic targets was performed in an automated fluidics station (Affymetrix FS450) as described in the Affymetrix Technical Manual, Revision 3. The arrays were transferred to the GCS3000 laser scanner (Affymetrix) and scanned at an emission wavelength of 570 nm at 2.5-mm resolution. Intensity of hybridization for each probe pair was computed by GCOS 1.1 software.

Exploratory data analysis was performed on the samples using R v2.2.0 and the add-on package affy v1.5.8 (14) (http://www.R-project.org). Background correction, normalization, and summarization were performed using Robust Multi-Array Analysis (14). Significance testing was performed with Significance Analysis of Microarrays (SAM) v2.21 to compare control samples with those obtained from children with measles at entry, discharge, and follow-up (46). A gene was considered significant if it had a change in expression of >2.0-fold and a false discovery rate (FDR) of <15% at the 90th percentile. SAM allows the investigator to choose the FDR, and with these parameters, no more than 15% of the genes identified as significant would be false discoveries. A more stringent FDR did not significantly alter the results. The genes were annotated with the 20 June 2005 Affymetrix release and grouped into gene ontologies (GO) with OntoExpress using the default settings (6). Only groups with corrected $P < 0.05$ and including five or more genes were considered in the analysis.

Cytokine and chemokine assays. Enzyme immunoassays (EIAs) for IL-1β, IL-8, CCL4, and CXCL2 were performed on stored plasma according to the manufacturers' protocols (R&D Systems and IBL-America, Minneapolis, MN). Plasma levels of IL-16 were previously determined by EIA (25).

Microarray data accession number. The microarray data are available at GEO under accession number GSE5808.

RESULTS

Leukocytes. WBC and differential counts were available for most children at each time point, and the percentages of $CD4^+$ and $CD8^+$ lymphocytes were determined on a subset of the samples (Fig. 1). WBC counts and the percentage of lymphocytes, $CD4^+$, and $CD8^+$ T lymphocytes closely resembled those reported for the larger study from which these samples were drawn (Fig. 1) (24). WBC counts were slightly elevated at discharge and follow-up with a lower lymphocyte percentage at entry and generally lower percentages of $CD4^+$ T cells compared to controls.

Gene expression. Microarray analysis was performed on mRNAs from PBMCs obtained from children with measles (see Table S1 in the supplemental material). There were no

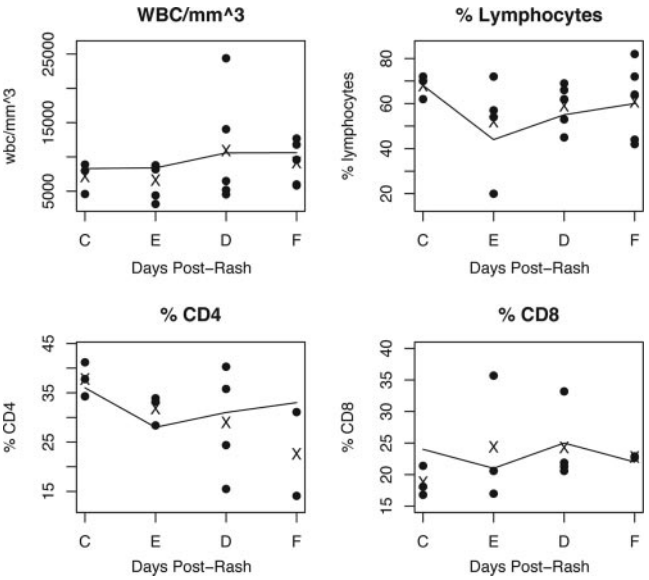

FIG. 1. WBC composition. The individual counts for each patient are shown with filled circles, and the mean values for the samples in this study are displayed with an "X." The means for the larger cohort are shown with a line connecting the sampling times. Data are shown for controls (C) and for children with measles at entry (E; days 2 to 7), discharge (D; days 4 to 11), and follow-up (F; days 36 to 61).

significantly regulated genes at entry, 224 at discharge, and 32 at follow-up. The results were pooled and duplicate genes were averaged, leaving 13 upregulated genes and 206 downregulated genes. Similar results were obtained by comparing controls versus days 2 to 4, 6 to 11, and 36 to 61. The significant groups with more than five genes for the GO biological processes annotation were identified. The only upregulated groups were signal transduction and apoptosis, which overlapped significantly. Upregulated genes included the cytokines IL-1β and tumor necrosis factor alpha (TNF-α), chemokines CCL4, CXCL2, and IL-8, cell surface molecules ICAM-1 and

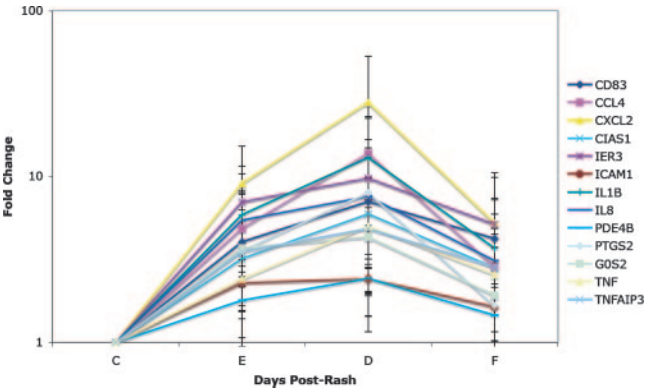

FIG. 2. Upregulated genes. The mean and standard deviation of the change in expression (*n*-fold) for each gene is shown. CIAS1, cold autoinflammatory syndrome 1 (NALP3); IER3, immediate early response 3 (IEX-1); ICAM1, intercellular adhesion molecule 1; PDE4B, phosphodiesterase 4B; PTGS2, prostaglandin-endoperoxide synthase 2; GOS2, putative lymphocyte G_0/G_1 switch gene; TNFAIP3, tumor necrosis factor α-induced protein 3 (A20); C, control; E, entry; D, discharge; F, follow-up.

TABLE 2. Significantly downregulated genes grouped by gene ontology (GO) biological process as analyzed using Onto-Express software

GO ID[c]	Function name	Unique input[a]	Corrected P^b
6355	Regulation of transcription, DNA dependent	35	0.0019
6350	Transcription	30	0.0012
7165	Signal transduction	24	0.038
6468	Protein amino acid phosphorylation	13	0.031
6955	Immune response	12	0.004
6357	Regulation of transcription from RNA polymerase II promoter	11	0.0025
398	Nuclear mRNA splicing, via spliceosome	7	0.018
7166	Cell surface receptor-linked signal transduction	6	0.019
19735	Antimicrobial humoral response (sensu Vertebrata)	6	0.0023
6968	Cellular defense response	5	0.0058

[a] Number of genes in each group.
[b] Probability that a finding is not due to chance after correcting for multiple comparisons.
[c] ID, identification.

CD83, and regulatory proteins CIAS-1 (NALP3), IER3 (IEX-1), PDE4B, PRGS2, GOS2, and TNFAIP3 (A20) (Fig. 2). These mRNAs increased at entry, peaked at discharge, and declined but remained above the control levels at follow-up.

The downregulated gene classifications fell into three broad GO biological process groups: transcription, signal transduction, and the immune response (Table 2). These gene expression levels were decreased at entry, and for most, the lowest expression levels were at discharge. There was a tendency to recover by follow-up, although not back to control levels (Fig. 3). The biological process group for transcription had the largest number of genes and included four classifications of downregulated genes: regulation of transcription, DNA-dependent (e.g., Sp3 transcription factor [Sp3], GATA binding protein 3 [GATA3], and lymphoid enhancer-binding factor 1 [LEF1]); transcription (e.g., BTB and CNC homology 1, basic leucine zipper transcription factor 2 [Bach2], Kruppel-like factor 2 [KLF2], and zinc finger protein 161 [ZNF161]); regulation of transcription from RNA polymerase II promoter (e.g., transcription factor 4 [TCF4], Kruppel-like factor 12 [KLF12], and Spi-B transcription factor [SPIB]); and nuclear mRNA splicing, via spliceosome (e.g., splicing factor 3a, subunit 2 and 3b, subunit 1 [SF3A2 and SF3B1] and RNA binding motif protein 14 [RBM14]). The largest gene groups in these classifications were zinc finger proteins ($n = 10$) and transcription factors ($n = 10$). The signal transduction biological process group included the classifications signal transduction, protein amino acid phosphorylation, and cell surface receptor-linked signal transduction. There were nine receptor genes and eight kinases in this group. The immune response biological process group included the classifications immune response, antimicrobial humoral response, and cellular defense response. Genes within these classifications included the cytokines IL-16 and TNFSF3 (LTβ) and the cytokine and chemokine receptors IL-4R, IL-6R, IL-7R, IL-27RA, CCR2, and CCR7 (Fig. 3).

Plasma cytokine and chemokine levels. To determine whether changes in mRNA expression levels resulted in altered plasma levels of cytokines or chemokines, EIAs were performed. IL-1β and IL-8 levels were significantly increased during acute measles (Fig. 4). IL-8 levels returned to baseline at follow-up, while IL-1β levels remained elevated. CXCL2 and CCL4 were both higher in controls than during acute infection. Plasma levels of IL-16 were lower at follow-up than at earlier times during infection and than in controls.

DISCUSSION

PBMCs are the most accessible tissue for analysis of gene expression during infectious disease in humans, but only a few infections have been studied. Examination of changes in gene expression in PBMCs from children with measles at hospital entry, discharge, and 1-month follow-up identified 13 upregulated genes and 206 downregulated genes. The upregulated genes tended to be genes regulated by NF-κB rather than by IFN and were consistent with an ongoing immune response. The downregulated genes were involved in cellular signaling and transcription and had not returned to control levels at follow-up. These gene expression patterns are consistent with, and help to explain, the prolonged alteration of lymphocyte responses characteristic of measles.

Remarkably, IFN-responsive genes were not upregulated and may have been actively suppressed. The function of one upregulated gene, TNFAIP3 (A20), is to downregulate the activity of IRF-3, a key transcription factor for induction of IFN (19, 38). This pattern is in contrast to the mRNAs increased by in vitro MV infection of dendritic cells and PBMCs that were predominantly IFN and IFN-responsive genes (3, 50). Likewise, PBMCs from influenza virus-infected humans and smallpox virus-infected monkeys showed significant upregulation of immune modulators induced by IFN (35, 36). However, PBMCs from patients with severe acute respiratory syndrome showed a similar pattern to measles with several upregulated genes from the innate immune system, but no IFN-induced genes (35). This suggests that gene expression in PBMCs during the phase of measles studied reflects primarily the immune response to infection, not infection per se. Because measles is not recognized until the rash appears as virus clearance is initiated 10 to 14 days after infection, and changes

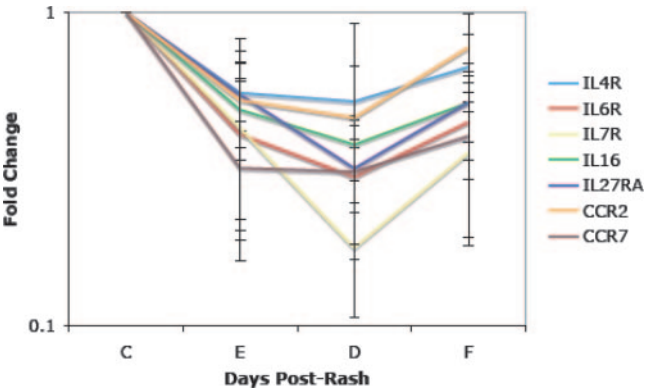

FIG. 3. Examples of downregulated immune response genes. The mean and standard deviation of the change in expression (n-fold) for each gene is shown. IL27RA, IL-27 receptor alpha chain (WSX-1); C, control; E, entry; D, discharge; F, follow-up.

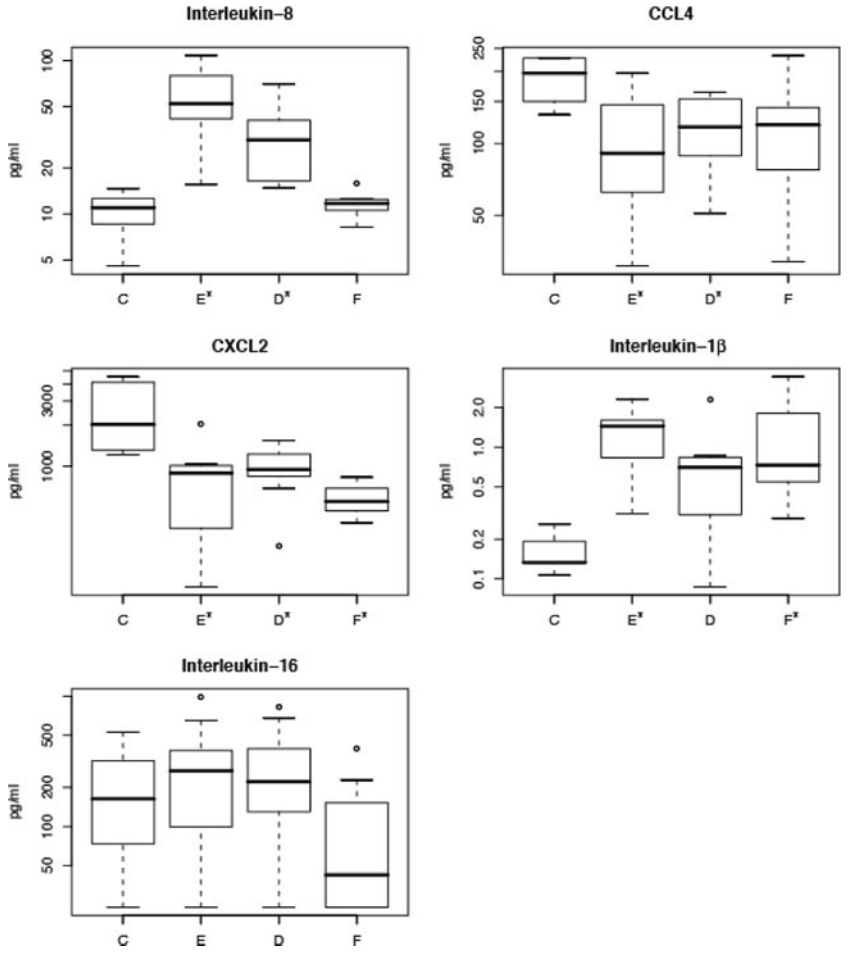

FIG. 4. Plasma levels of chemokines and cytokines. Box plots of plasma protein levels of IL-8, CCL4, CXCL2, IL-1β, and IL-16, as measured by EIA, are shown. Time points with $P < 0.05$ relative to the control level are indicated by an ∗. IL-16 plasma levels were previously reported for this cohort (25).

in gene expression are rapid and tightly controlled (3, 4, 50), it is possible that an IFN response would have been detected earlier in infection.

Although changes in gene expression were not statistically significant until discharge, the patterns of expression of both up- and downregulated genes were established at entry. The lack of statistical significance is probably related to the greater variability at this time of rapid change related to initiation of the immune response. In addition, the mRNAs for several proteins that are significantly increased or decreased in plasma during measles virus infection (e.g., IL-2, IL-4, IL-10, and IL-12) (1, 26, 29, 34) were not identified as regulated. This could be because PBMCs are not the main source of these cytokines, because regulation is not at the level of transcription, or because the criteria used for gene identification missed biologically relevant changes in PBMC gene expression.

Among the upregulated genes were proinflammatory cytokines IL-1β and TNF-α. IL-1β mRNA and protein production are also upregulated in MV-infected monocyte-derived cells and cultured PBMCs taken from patients during the convalescent phase of infection (18, 49). Production of biologically active IL-1β is only partially regulated at the transcriptional level, as the mRNA is translated as a leaderless 35-kDa precursor protein that must be processed by caspase-1 to the active secreted form. IL-1β processing is regulated within the "inflammasome," a complex of the proteins CIAS-1 (NALP3), Cardinal, ASC, and pro-IL-1β (28, 44). CIAS-1 mRNA was also upregulated during measles virus infection and IL-1β protein was increased in the plasma of the children studied, documenting the biologic relevance of the increased expression of these genes. A previous study did not detect IL-1β in serum, but the assay may have lacked sensitivity (29).

Cell surface molecules that were upregulated included ICAM-1 and CD83. ICAM-1 is induced on activated lymphocytes and monocytes and enhances both antigen presentation and vascular adhesion (16). CD83 is a marker of mature dendritic cells and regulates the development of cellular immune responses (17, 41).

There were several chemokines significantly upregulated during measles virus infection, specifically CCL4 (MIP-1β), CXCL2 (GRO-β), and CXCL8 (IL-8). CCL4 is produced at sites of interaction between antigen-specific dendritic cells and $CD4^+$ T cells and attracts naïve $CD8^+$ T cells that express CCR5 (5, 22, 32). CXCL2 and IL-8 are structurally related

GRO family chemokines that are produced by macrophages (42). Both IL-8 and CXCL2 bind to CXCR2, but IL-8 also binds to CXCR1 expressed on a subset of effector CD8 T cells (12, 45). CXCL2 may contribute to lung injury during viral infection (20). Infection of epithelial cells with a number of respiratory viruses, including MV, increases expression of IL-8 in vitro (40). IL-8 is increased in the plasma of monkeys early after MV infection (40) and, in this study, was increased in children with measles during the rash. However, CCL4 and CXCL2 plasma levels were lower during acute infection, suggesting that the changes seen in PBMCs may have local effects that were not reflected in plasma.

Expression of many more genes was decreased than increased, and these decreased mRNAs encoded proteins involved in signaling and regulation of transcription. In contrast, in lipopolysaccharide-challenged humans, the downregulated genes were involved in respiration, protein synthesis, and degradation (4), and in smallpox virus-infected monkeys, the downregulated genes were T and B cell markers and reflected lymphopenia. Acute measles changes were most similar to those induced by chronic HIV-1 infection in humans, where genes associated with signal transduction, immune response, and transcription were also largely downregulated (27). Simian immunodeficiency virus-infected macaques sampled at 3 and 7 weeks after infection had two downregulated zinc finger proteins similar to measles but otherwise showed quite different responses with few downregulated genes (47). Although the cell composition of the PBMC compartment is changing during measles virus infection, we do not think that this had a significant effect on the results, because the largest alterations in cell composition occurred at entry. This fact may have contributed to the variability and lack of significantly regulated genes at this time.

Among the downregulated genes was the CD4 chemotactic cytokine IL-16, and this was reflected in decreased IL-16 plasma levels at follow-up (7, 25). Several receptors for cytokines and chemokines were downregulated: IL-4R, IL-6R, IL-7R, IL-27RA, CCR2, and CCR7. CCR2, the receptor for MCP1 (CCL2), MCP3 (CCL7), and MCP5 (CCL12), is highly expressed on monocytes and is downregulated when monocytes differentiate into macrophages (21, 31). Both TLR2 and TLR4 agonists downregulate CCR2, and the MV H protein can activate TLR2 (2, 30). CCR7 is important for dendritic cell and T cell homing to lymph nodes and is upregulated early after MV infection of dendritic cells (50) but is absent on effector memory cells (15), which express receptors necessary for migration to inflamed tissues. This decrease is consistent with an ongoing T cell effector response during the rash phase of measles (9, 39). Also consistent with an effector memory response is the increase in phosphodiesterase-4 (PDE4B) that is expressed at high levels in memory $CD4^+$ T cells, where it regulates degradation of cyclic AMP, a mediator of inflammatory responses (43).

In summary, the gene expression patterns during the rash and convalescent phase of measles reflect ongoing immune responses and extensive downregulation of signaling and transcription pathways that are likely to underlie the inability of lymphocytes to respond to stimuli, such as tuberculin, with a delayed type hypersensitivity response or to mitogens with proliferation.

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