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Constitutive Differences in Gene Expression Profiles Parallel Genetic Patterns of Susceptibility to Tuberculosis in Mice¶

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Interstitial lung macrophages from tuberculosis-susceptible I/St and tuberculosis-resistant A/Sn mice demonstrated significant constitutive differences in gene expression levels, whereas in vitro infection of these cells with *Mycobacterium tuberculosis* had only a modulatory impact on gene expression. We conclude that intrinsic gene expression profiles are an important determinant of tuberculosis pathogenesis in mice.

The primary host cells for *Mycobacterium tuberculosis*, which is the causative agent of tuberculosis (TB), are mature tissue macrophages. The specific host response pathways allowing *M. tuberculosis* to take up residence in macrophages and the host cell factors that underlie the *M. tuberculosis*-macrophage interplay are largely unknown. We have previously demonstrated that in A/Sn and I/St mice, which are genetically resistant and susceptible to tuberculosis, respectively (7, 16), only freshly isolated interstitial lung macrophages, and not peritoneal or spleen- or bone marrow-derived macrophages, strictly followed the genetic pattern of tuberculosis susceptibility/resistance (11). In addition, the resistance phenotype can be readily transferred with bone marrow cells from resistant F_1 donors into irradiated susceptible I/St recipients (12). To further identify host response genes involved in early *M. tuberculosis*-macrophage interactions, we conducted a series of microarray gene expression experiments employing lung macrophages from A/Sn and I/St mice.

Interstitial lung macrophages, isolated as described earlier (11), were either infected with *M. tuberculosis* H37Rv at a multiplicity of infection of 5:1 for 24 h or cultured under the same conditions without infection (control). The efficiency of infection was 50% to 60%, as demonstrated by auramine staining of fixed macrophages, with no observed interstrain difference in mycobacterial uptake (data not shown). RNA extracted from infected and control macrophages of I/St and A/Sn mice (RNeasy minikit; QIAGEN, California) was hybridized to murine genome U74Av2 microarrays (www.affymetrix.com). The data were analyzed with the Significance Analysis of Microarrays software (SAM; http://www-stat.stanford.edu/~tibs/SAM//index.html). For the analysis, the gene expression levels in macrophages of I/St and A/Sn mice were compared either before or after infection. We considered genes that had *d* scores (absolute values) of ≥2.0 to be significant. The *d* score is similar to a *t* statistic, but a small constant is added to the standard error to reduce the variability in its estimate. A better measure of statistical significance can be obtained by examining the false detection rate (FDR) associated with the magnitude of the differences between strains, with adjustment for the number of genes tested (24). Accurate empirical estimates of the FDR were obtained from the permutation analysis built into the SAM software, employing a *d* score (absolute value) of 2.0 corresponding to an estimated FDR of 1% (24). Microarray data analysis led to the identification of 152 genes with significant differentials in expression either before or after infection of lung macrophages of the two strains (Table 1; see also supplemental material S1).

Generally, lung macrophages from susceptible I/St mice demonstrated significantly higher expression levels of cytokine/chemokine genes, including the genes for interleukin 11 (*Il-11*), *Il-6*, *Cxcl-13*, and *Cxcl-14* (Table 1), than did their A/Sn counterparts. In contrast, only three cytokine/chemokine genes (*Cxcl-10*, *Cxcl-9*, and *Il-17*) were expressed at significantly higher levels in macrophages from resistant A/Sn mice. In the group of immune response genes, I/St macrophages expressed only three genes (*Ifi205*, *Ifi202*, and *Saa3*) at a higher level than did A/Sn macrophages. Conversely, a large number of genes belonging to this class were expressed at significantly higher levels in A/Sn macrophages (Table 1), suggesting their critical role in the development of the immune response at an early stage of infection. The majority of genes encoding receptor/cell surface molecules that are potentially important for the on-time activation of protective mechanisms after infection were highly expressed in lung macrophages of A/Sn mice. Likewise, genes encoding signal transduction molecules were generally expressed at higher levels in A/Sn macrophages (see supplemental material S1). Interestingly, matrix metalloproteinase 8, one of the extracellular matrix proteins involved in the processing of extracellular matrices and wound healing (20), was shown to be expressed at significantly higher levels in A/Sn

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TABLE 1. Partial list of genes differentially expressed in I/St and A/Sn macrophages[a]

Gene	Score (*d*) for[b]: Control cells[c]	Score (*d*) for[b]: Infected cells[d]	Protein or gene[e]	Accession no.	Gene name
Chemokine and cytokine genes					
Scyb14[f]	10.4	5.3	Cxcl14, macrophage inflammatory protein 2 gamma	AW120786	96953_at
Il-11[f]	9.9	3.4	Interleukin 11	U03421	92266_at
Scyb13[f]	7.4	6.1	Cxcl13, B-cell homing chemokine	AF030636	102025_at
Ccr5	NS	2.4	Chemokine (C-C motif) receptor 5	AF022990	161968_f_at
Scya11	3.6	NS	Small chemokine (C-C motif) ligand 11 (eotaxin-1)	U77462	92742_at
Il-6[f]	3.5	NS	Interleukin 6	X54542	102218_at
Scyb2 MIP-2a	3.2	NS	Cxcl-2, macrophage inflammatory protein 2 alpha	X53798	101160_at
Scyb1 MIP-2	2.8	NS	Cxcl-1, macrophage inflammatory protein 2	L12030	95349_g_at
Il-17	−5.6	NS	Interleukin 17	U35108	99349_at
Scyb10	−3.0	NS	Cxcl-10, macrophage interferon-activated protein 10 (IP-10)	M33266	93858_at
Scyb9	−2.9	NS	Cxcl-9, monokine induced by gamma interferon (Mig)	M34815	101436_at
Immune response genes					
Ifi205	7.7	3.0	Interferon-activated gene 205	M74123	94224_s_at
Ifi202a	5.3	2.0	Interferon-activated gene 202A	AV229143	94774_at
Saa3[f]	5.0	3.5	Serum amyloid A 3	X03505	102712_at
Gbp2	−4.8	−2.0	Guanylate nucleotide binding protein 2	AJ007970	104597_at
Chi3l3	NS	3.9	Chitinase 3-like 3	M94584	92694_at
Gbp1	−5.1	NS	Guanylate nucleotide binding protein 1	M55544	95974_at
Psmb9	−4.8	NS	Proteosome (prosome macropain) subunit beta type 9	D44456	93085_at
Ifit2	−4.4	NS	Interferon-induced protein with tetratricopeptide repeats 2	U43085	103639_at
Mx2	−4.2	NS	Myxovirus (influenza virus) resistance 2	J03368	102699_at
Gbp3	−3.4	NS	Guanylate nucleotide binding protein 3	AW047476	103202_at
Mx1	−3.4	NS	Myxovirus (influenza virus) resistance 1	M21038	98417_at
Ifi47	−3.2	NS	Gamma interferon-inducible protein	M63630	104750_at
Cytoskeletal/extracellular matrix genes					
Mglap	3.9	2.4	Matrix gamma-carboxyglutamate (gla) protein	D00613	93866_s_at
Csrp1	NS	2.9	Cysteine-rich protein 1	D88793	92608_at
Adam8	NS	2.7	A disintegrin and metalloprotease domain 8	X13335	103024_at
Coro1a	NS	2.1	Coronin actin binding protein 1A	AW122039	96648_at
Mmp8[f]	NS	−2.4	Matrix metalloproteinase 8	U96696	94769_at
Cldn4	3.2	NS	Claudin 4	AB000713	101410_at
Receptor/cell surface genes					
Fpr1	5.2	2.3	Formyl peptide receptor 1	L22181	99387_at
Tm7sf1	−6.7	−7.0	Transmembrane 7 superfamily member 1	AI060729	103017_at
Marco	−5.1	−2.1	Macrophage receptor with collagenous structure	U18424	102974_at
Cd22	−5.0	−3.0	CD22 antigen	L02844	102939_s_at
Il-7r	−3.6	−5.5	Interleukin 7 receptor	M29697	99030_at
Il1rl1	NS	−2.5	Interleukin 1 receptor-like 1	Y07519	98501_at
Taa1	7.8	NS	Tumor-associated antigen 1	U35836	94643_at
Tnfrsf9	4.6	NS	Tumor necrosis factor receptor superfamily member 9	AA798611	103509_at
Bdkrb	3.6	NS	Bradykinin receptor beta	L26047	101748_at
Raet1c	3.3	NS	Retinoic acid early transcript gamma	D64162	102649_s_at
Pira1	3.1	NS	Paired-immunoglobulin-like receptor A1	U96682	95784_at
Ly6a	−4.3	NS	Lymphocyte antigen 6 complex locus A	X04653	93078_at
Itpr5	−3.2	NS	Inositol 145-triphosphate receptor 5	AF031127	101441_i_at
Ifngr	−3.2	NS	Gamma interferon receptor	M28233	99334_at
Csf2rb1	−3.0	NS	Colony-stimulating factor 2 receptor beta 1	M34397	94748_g_at

[a] Expression levels of genes in I/St macrophages are given relative to A/Sn macrophages, with negative numbers indicating that the gene is expressed at a higher level in A/Sn macrophages.
[b] NS, not significant.
[c] Relative interstrain difference in gene expression in uninfected macrophages.
[d] Relative interstrain difference in gene expression in infected macrophages.
[e] Protein name abbreviation is given in case it differs from the gene name.
[f] Results for these genes were confirmed by quantitative real-time assay.

TABLE 2. Real-time reverse transcription-PCR confirmation of array data

Gene	In vitro infection with *M. tuberculosis*	Expression level for I/St vs A/Sn macrophages	
		PCR[a]	Microarray[b]
Il-11	−	8.9	5.0
	+	7.6	3.7
Il-6	−	3.6	2.1
	+	4.5	2.2
Mmp8	−	−3.4[c]	NS[d]
	+	−5.4	−2.1
Cxcl14	−	11.1	4.2
	+	9.6	3.5
Cxcl13	−	28.1	5.1
	+	30.7	7.2
Saa3	−	9.3	2.5
	+	12.3	2.3

[a] Mean fold change in expression level for three experiments.
[b] Fold change in gene expression revealed by SAM analysis of three microarray hybridization sets.
[c] Negative numbers indicate that the gene is expressed at a higher level in A/Sn macrophages.
[d] NS, not significant.

macrophages. Differences in constitutive expression levels for selected genes (*Il-11*, *Il-6*, *Mmp8*, *Cxcl-14*, *Cxcl-13*, and *Saa3*) were confirmed by real-time reverse transcription-PCR (RT-PCR) (Table 2; see also supplemental material S2) using mRNAs obtained in three additional independent experiments.

Constitutive higher expression of *Il-6* by macrophages of susceptible I/St mice is consistent with the data of Keller and colleagues, who demonstrated an approximately 10-fold increase in *Il-6* expression in infected macrophages from TB-susceptible but not from TB-resistant mice (10). IL-6 is a pleiotropic cytokine which is produced by a variety of cells, including macrophages (14, 26), with numerous types of cell targets. *M. tuberculosis*-infected macrophages produce IL-6, which inhibits gamma interferon-responsive genes in macrophages and inhibits eradication of infection (14).

Remarkably, the high expression level of *Il-6* by macrophages of I/St mice is accompanied by elevated levels of *Cxcl-13* (*Scyb13*) expression (Tables 1 and 2). Cxcl-13, the B-cell-homing chemokine, is produced by macrophages (2, 9) and dendritic cells (3). Goya and colleagues (8) have shown that prolonged production of IL-6 in the lungs leads to formation of pulmonary lesions that have lymphoid tissue-like structure, where the chemokine gene *Cxcl-13* is highly expressed. Significantly higher expression levels of *Il-6* and *Cxcl-13* by lung macrophages of susceptible I/St mice (Tables 1 and 2), in conjunction with extremely high levels of specific immunoglobulin G2a antibody responses in these mice (18), strongly suggest that severe TB inflammation in the lungs of these mice involves a nonprotective B-cell component. This suggestion is further supported by a recent finding of Ulrichs et al. (25), who demonstrated the formation of well-organized B-cell foci in the vicinity of tuberculous lesions in lung tissue surgically removed from TB patients with a rapidly progressing severe form of the disease.

An exciting new finding obtained in this study is the high level of *Il-11* expression by lung macrophages. IL-11 is a pleiotropic cytokine with anti-inflammatory activity when expressed at moderate levels (23, 27), but its overexpression may have a significant proinflammatory effect (22, 28). The production of IL-11 had previously been described for lung fibroblasts, airway epithelial cells (5, 6), and antigen-presenting cells after infection with respiratory syncytial virus (1). To demonstrate that *Il-11* is indeed expressed by lung macrophages and not by contaminating lung fibroblasts, we developed fibroblast cultures from lung stroma of I/St and A/Sn mice and compared the levels of expression of *Il-11* and *Cxcl-14* in these cells and in interstitial lung macrophages. *Cxcl-14* is the mouse ortholog of the human breast- and kidney-expressed chemokine gene (*BRAK*) and is constitutively expressed by fibroblasts in a number of mouse organs, including lungs. The results of this comparison are presented in Fig. 1. I/St and A/Sn lung macrophages expressed, respectively, 60- and 30-fold-higher levels of *Il-11* than their corresponding lung fibroblasts. Conversely, I/St and A/Sn lung fibroblasts expressed 8- and 50-fold-higher levels of *Cxcl-14* than their corresponding lung macrophages. These results show that lung macrophages are major producers of *Il-11* and that the high expression levels of *Il-11* in macrophages of tuberculosis-susceptible I/St mice compared to expression levels of *Il-11* in tuberculosis-resistant A/Sn mice offer a possible explanation for the development of severe pathology in the lungs of *M. tuberculosis*-infected I/St mice (7, 16, 18).

While several studies have analyzed the response of host

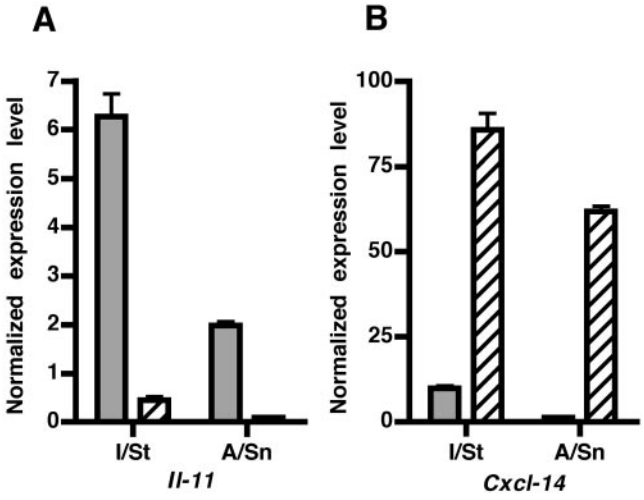

FIG. 1. Expression of *Il-11* and *Cxcl-14* by lung macrophages and fibroblasts isolated from TB-susceptible I/St mice and TB-resistant A/Sn mice. Normalized *Il-11* and *Cxcl-14* gene expression levels are shown as severalfold differences relative to *Hprt* gene expression. (A) Lung macrophages (gray bars) express higher levels of *Il-11* than lung fibroblasts (hatched bars) from both I/St and A/Sn mice. (B) Lung fibroblasts (hatched bars) express higher levels of *Cxcl-14* than macrophages (gray bars) from mice of both strains. In each experiment, syngeneic lung macrophages or lung fibroblasts extracted from several mice were pooled. Expression levels of *Il-11* and *Cxcl-14* were measured by quantitative RT-PCR. Results are expressed as means (±standard errors) of triplicate assays from one of three experiments with similar results.

macrophages to mycobacterial infection (4, 10, 13, 15, 17, 19, 21,), none of these studies employed ex vivo-isolated lung macrophages, the predominant cell type naturally infected with *M. tuberculosis*, and only one study used a combination of resistant and susceptible strains of mice (10). However, all of these studies reported significant *M. tuberculosis*-triggered host gene expression changes. Surprisingly, we did not observe major changes in gene expression by lung macrophages of either I/St or A/Sn mice following 24-h infection with *M. tuberculosis* H37Rv. Hence, we tested whether overly conservative criteria for significant gene expression changes underlie this finding. It appeared that even a reduction in stringency of the analysis with an FDR up to 75% did not allow the reproduction of previously reported results (4, 10, 13, 17, 21). In a final set of experiments, we selected eight genes (*Il-6*, *Saa3*, *Slpi*, *Ccl5*, *Cxcl-5*, *Cxcl-10*, *Mrc1*, and *Mmp9*) that had been reported to undergo significant expression changes following *M. tuberculosis* infection of murine bone marrow-derived macrophages (4, 21, 10, 17). We found that infection of interstitial lung macrophages with *M. tuberculosis* does not lead to changes in the expression level of these genes (change of ≤1.5-fold [absolute value]) (data not shown). These results support the hypothesis that different types of macrophages respond differently to *M. tuberculosis* infection and argue against the suggestion that too-stringent criteria had been used in the microarray analysis.

In summary, by employing global analysis of gene expression, we observed a statistically well-defined signature of gene expression differences among interstitial macrophages from A/Sn and I/St mice. These interstrain gene expression differences provide a rational basis for a mechanistic framework of the genetically controlled tuberculosis resistance and susceptibility displayed by A/Sn and I/St mice. By contrast, we were unable to reveal significant *M. tuberculosis*-triggered gene expression changes in interstitial lung macrophages. It is possible that the in vitro infection experiments are not a correlate of the response of the whole animal. This possibility appears unlikely since lung macrophages faithfully repeat the pattern of resistance and susceptibility observed at the whole-animal level. It is more likely that intrinsic gene expression levels are an important determinant of TB pathogenesis in the mouse and that constitutive genetically controlled gene expression in lung macrophages is an area that requires more careful consideration in the study of TB pathogenesis.

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