Flagellin Induces Myeloid-Derived Suppressor Cells: Implications for Pseudomonas aeruginosa Infection in Cystic Fibrosis Lung Disease

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FlagellinInducesMyeloid-DerivedSuppressorCells:
ImplicationsforPseudomonas aeruginosainCystic
FibrosisLungDisease

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Pseudomonas aeruginosais a gram-negative flagellated bacterium, acts as opportunistic pathogen in immunocompro-
mised hosts or compartments in which the local host defense is impaired. P. aeruginosapotently activates the innate arm of the immune system, an effect mainly mediated through pathogen-
associated molecular patterns (PAMPs) and pattern recognition receptors. Among those, the TLR 5 ligand flagellin was found to play

a key role in the recognition of P. aeruginosais (1–5). However, patients with chronic lung diseases, prototypically cystic fibrosis (CF) patients (6), are unable to eradicate the bacterium efficiently. The underlying immunological mechanisms are poorly understood. P. aeruginosais known to suppress T cell responses in vivo, and lymphocytes isolated from P. aeruginosainfected CF patients show a blunted T cell proliferation capability ex vivo (7, 8). Beyond direct effects of P. aeruginosais on T cells (7, 8), this flagellated bacterium activates TLR5 on innate myeloid cells. Myeloid-derived suppressor cells (MDSCs) represent a novel innate immune cell subset generated in tumor, infective, and proinflammatory micro-

environments (9, 10). These specialized innate immune cells are characterized by their capacity to suppress T cell responses and thereby modulate the cellular arm of adaptive immunity (10). Consequently, MDSCs are considered a key intermediary in balancing innate and adaptive immune responses, particularly under chronic disease conditions. In mice, in which MDSCs have been studied extensively, these cells constitute both a neutrophilic and monocytic MDSC subphenotype (10–12); studies on MDSCs in human disease conditions are scarce. Recent evidence suggests that neutrophilic MDSCs accumulate in malignancy and systemic inflammation and are capable of suppressing T cell responses (13–15), but their role in host–pathogen interactions is, so far, poorly understood.

On the basis of the fact that CF patients are unable to eradicate P. aeruginosainfections and show impaired T cell proliferation, we hypothesized that P. aeruginosais induces MDSCs to escape T cell immunity. Our studies demonstrate that neutrophilic MDSCs are induced in P. aeruginosa-infected CF patients and correlate with

The online version of this article contains supplemental material.

Abbreviations used in this article: CF, cystic fibrosis; CFTR, cystic fibrosis trans-
membrane conductance regulator; FEV1, forced expiratory volume in 1 s; MDSC, myeloid-derived suppressor cell; MEF25, maximum expiratory flow rate at 25% of vital capacity; PAMP, pathogen-associated molecular pattern.

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pulmonary disease. Flagellated *P. aeruginosa* culture supernatants as well as purified flagellin dose-dependently and efficiently induced MDSC generation, corresponding to TLR5 expression on MDSCs. Functionally, both CF patient–isolated and flagellin-induced MDSCs suppressed T cell proliferation and modulated Th17 cells, as key antibacterial T cell populations in CF. This study highlights a novel mechanism by which the flagellated bacterium *P. aeruginosa* subverts host defense by inducing T cell–suppressive MDSCs. Given the well-documented role of this cell type in immune regulation, MDSCs could therefore represent a novel therapeutic target in CF and other diseases characterized by infections with flagellated bacteria.

**Materials and Methods**

**Study subjects**

The study was conducted at the University Children’s Hospital Tübingen (Tübingen, Germany). MDSCs were analyzed in the peripheral blood of patients with CF (*n* = 75) and age-matched pediatric non-CF control subjects without infections, malignancies, or inflammation (*n* = 37) (Table I). Informed written consent was obtained from all subjects included in the study or their legal representatives, and all study methods were approved by the local ethics committee. Inclusion criteria were the diagnosis of CF by clinical symptoms and positive sweat tests (sweat Cl– concentration > 60 mmol/l) or disease-causing mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Chronic *P. aeruginosa* infection was diagnosed if the organism was isolated in at least two consecutive sputum samples with a minimum interval of 6 mo. For lung function analyses, diagnosed if the organism was isolated in at least two consecutive sputum samples with a minimum interval of 6 mo. For lung function analyses, diagnosed if the organism was isolated in at least two consecutive sputum samples with a minimum interval of 6 mo.

**Cell isolation and flow cytometry**

PBMCs were prepared from blood samples by Ficoll density gradient sedimentation (Lymphocyte Separation Medium; Biochrom) and washed twice in RPMI 1640 medium. Trypan blue staining solution at 0.5% differentiated between viable and nonviable cells and showed viability of >90% for all cells used in this study. After Ficoll density gradient sedimentation, MDSCs were characterized as CD33highCD66bhighIL-4RamanIL-4Ra–HLA-DRdim neutrophilic cells in the PBMC fraction, according to previously established human MDSC analysis methods (13, 15) (Fig. 1). For MDSC isolation, cells were obtained from the PBMC fraction and labeled with anti–CD66b-APC, followed by two sequential anti-FITC magnetic bead separation steps (Miltenyi Biotech), per the manufacturer’s protocol. Purity of CD66b+ cells after separation was >95%, as assessed by flow cytometry. Morphology of the cells (MDSCs and conventional neutrophils isolated from healthy control individuals) was performed by staining of cytospins. Isolated MDSCs showed typical morphological characteristics of neutrophils, marking them as neutrophilic MDSCs (see supplementary material). For cytospin stainings, 5 × 10^5 cells were centrifuged in a Cytospin 3 Centrifuge (Shandon) at 800 rpm for 15 min and stained with May–Gruenwald–Giemsa. Abs against CD3, CD4, CD8, CD14, CD16, CD66b, HLA-DR, and CD124 (IL-4Rα) were purchased from BD Pharmingen. Abs against CD11b and CD33 were purchased from Miltenyi Biotec. Anti-human CXCR4 (clone 12G5) was obtained from eBioscience (San Diego, CA). Abs against TLR5 were purchased from Santa Cruz Biotechnology. Mouse IgG1-FITC, Mouse IgM–FITC, Mouse IgG1-PE, and Mouse IgG1-APC (BD Pharmingen) were used as isotype controls. Results were expressed as percent of positive cells and mean fluorescence intensity. Calculations were performed with BD CellQuest analysis software. For Th17 cell staining, 2.5 × 10^6 PBMCs were stimulated overnight with 10 ng/ml PMA and 1 μg/ml ionomycin (Sigma-Aldrich, St Louis, MO) in the presence of GolgiPlug (BD Biosciences, San Jose, CA). After cell surface staining with PE-conjugated anti-CD4 (eBioscience), cells were fixed and permeabilized (Cytofix/Cytoperm; BD Biosciences) and stained with Alexa Fluor 647–conjugated anti–IL-17A (eBioscience). As a control for cellular activation and intracellular staining, CD4+ T cells were also evaluated for IFN-γ production (FITC–conjugated; eBioscience). For all in vitro FACS assays, three independent experiments were performed.

**In vitro generation and isolation of human MDSCs**

Human MDSCs were generated in vitro according to a previously published protocol (16). Isolated human PBMCs were cultured in 12-well flat-bottom plates (Corning) or 25-cm² flasks (Greiner Bio-One) at 5 × 10^5 cells/ml in complete medium for 6 d, and GM-CSF (10 ng/ml; Genzyme), *P. aeruginosa* concentration 2.5 × 10^6 PBMCs were stimulated overnight with 10 ng/ml PMA and 1 μg/ml ionomycin (Sigma-Aldrich, St Louis, MO) in the presence of GolgiPlug (BD Biosciences, San Jose, CA). After cell surface staining with PE-conjugated anti-CD4 (eBioscience), cells were fixed and permeabilized (Cytofix/Cytoperm; BD Biosciences) and stained with Alexa Fluor 647–conjugated anti–IL-17A (eBioscience). As a control for cellular activation and intracellular staining, CD4+ T cells were also evaluated for IFN-γ production (FITC–conjugated; eBioscience). For all in vitro FACS assays, three independent experiments were performed.

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culture supernatants (0.1–1%), flagellin (0.0001–0.1 μg/ml; Invivogen), or the CFTR inhibitors CFTRinh-172 (10 μM; Tocris) or GlyH-101 (10 μM; Merck, Millipore) were added as indicated in the respective figures. For all assays, at least three independent experiments were performed. P. aeruginosa culture supernatants were generated from two flagellated (PAO1 and PA14) strains or from a flagellin-deficient (PAO1 fliM) strain according to standard protocols. PBMCs cultured in medium alone were run in parallel as a control for each donor. Medium and supplements were refreshed after 3 d. After 6 d, all cells were collected from PBMC cultures. Adherent cells were removed using the nonprotease cell detachment so-

FIGURE 2. Increased MDSCs in chronic P. aeruginosa infection. (A) Percentages of MDSCs in healthy control subjects (white circles) and in CF patients (gray circles). (B) Percentages of MDSCs in non-P. aeruginosa-infected (white bar) and P. aeruginosa-infected (black bar) CF patients. (C and D) Correlation between percentages of MDSCs and obstructive lung function parameters (FEV1 and MEF25) in non-P. aeruginosa-infected (left panel) and P. aeruginosa-infected (right panel) CF patients. *p < 0.05.
CD4 and CD8 T cell proliferation was analyzed (Supplemental Fig. 2C). AMD3100 (2 μM; Sigma-Aldrich), on MDSC-mediated suppression of their capacity to induce MDSC generation in vitro. These studies demonstrated that P. aeruginosa culture supernatants from two different P. aeruginosa strains efficiently induced MDSCs to a similar extent as GM-CSF did, which is well demonstrated that P. aeruginosa and other characteristic pathogens in CF lung disease, suggesting that the accumulation of MDSCs in CF patients is not due to infection in general but indicates that P. aeruginosa–associated factors induce MDSCs and thereby modulate lung disease severity in CF.

Flagellated Pseudomonas aeruginosa and purified flagellin induce CXCR4high MDSCs

To test our hypothesis that P. aeruginosa–derived factors, such as microbe-associated or shedded PAMPs (6), in CF patients drive the generation of MDSCs, we first used P. aeruginosa culture supernatants from two different P. aeruginosa isolates (Supplemental Fig. 1A). Importantly, percentages of MDSCs increased in P. aeruginosa–infected, but not in non–P. aeruginosa–infected, conditions, and also suggested that MDSCs correlate with lung function over time (Supplemental Fig. 1B). No statistical association of antibiotics with MDSCs was found. Despite a substantial number of CF patients colonized with P. aeruginosa and Staphylococcus aureus (15 of 29, see Table I for details), no statistical associations were found between MDSC percentages and the detection of S. aureus or Aspergillus fumigatus.

### Table I. CF patient and control group

<table>
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<tr>
<th>Parameters</th>
<th>Cystic Fibrosis</th>
<th>Controls</th>
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<tr>
<td>N</td>
<td>75</td>
<td>37</td>
</tr>
<tr>
<td>Age (y)</td>
<td>16 ± 10</td>
<td>14 ± 12</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>38/37</td>
<td>21/16</td>
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<tr>
<td>WBC (10⁹/l)</td>
<td>8 ± 2</td>
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<tr>
<td>CRP (mg/dl)</td>
<td>0.41 ± 0.76</td>
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<tr>
<td>FVC (% pred.)</td>
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<td>FEV₁ (% pred.)</td>
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</tr>
<tr>
<td>MEF₂⁵ (% pred.)</td>
<td>56 ± 30</td>
<td>ND</td>
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<tr>
<td>P. aeruginosa⁺</td>
<td>29 ND</td>
<td>ND</td>
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<tr>
<td>S. aureus⁺</td>
<td>49 ND</td>
<td>ND</td>
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<td>P. aeruginosa/S. aureus coinfection</td>
<td>15</td>
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</tr>
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<td>Age P. aeruginosa</td>
<td>22 ± 11</td>
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<tr>
<td>Age S. aureus</td>
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<tr>
<td>dS508homozygous/heterozygous/other</td>
<td>29/31/15 ND</td>
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</tr>
</tbody>
</table>

Results are expressed as means ± SD.

⁺P. aeruginosa bacteria isolated in at least two consecutive sputum samples or throat swabs with a minimum interval of 6 mo.

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% pred., % of predicted; CRP, C-reactive protein; f, female; FVC, forced vital capacity; m, male.
Flagellated *P. aeruginosa* bacteria and purified flagellin protein induce MDSCs. (A) Flagellated *P. aeruginosa* induces MDSCs. MDSCs were generated by incubating PBMCs with medium only (negative control), GM-CSF (10 ng/ml, positive control), or two different flagellated *P. aeruginosa* strain (PAO1 or PA14) derived culture supernatants at 0.1 or 1% medium culture conditions. The x-fold induction of MDSCs compared with control conditions is depicted. (B) Flagellin induces MDSCs. The effect of purified flagellin (for concentrations, see figure) or GM-CSF (10 ng/ml) on MDSC generation is depicted. The x-fold induction of MDSCs compared with control conditions is depicted. (C) *P. aeruginosa* induces MDSCs through flagellin. MDSCs were generated by incubating PBMCs with medium only (negative control), with GM-CSF (10 ng/ml, positive control) or with culture supernatants (1% medium culture conditions) from a flagellated *P. aeruginosa* strain (PAO1) or a matched nonflagellated strain (PAO1 fliM mutant strain). The x-fold induction of MDSCs compared with control conditions is depicted. (D) MDSCs express TLR5. MDSCs were generated in vitro by incubating isolated PBMCs with *P. aeruginosa* PAO1 (1%) derived culture supernatants (“MDSC in vitro”). TLR5 expression on CF patient ex vivo–isolated (Figure legend continues).
To dissect which mechanism(s) induce(s) MDSCs in chronic *P. aeruginosa* infection, we focused on flagellin because 1) infection with flagellated *P. aeruginosa* was associated with MDSC induction in our CF patient cohort, whereas nonflagellated microbes did not show any association with MDSCs in vivo; and 2) previous studies showed that among different PAMPs, flagellin recognition through TLR5 in particular plays a key role in leukocyte-*P. aeruginosa* interactions in CF lung disease (4, 5, 17, 18).

Our studies demonstrated that flagellin efficiently and dose-dependently induced MDSCs with a more potent capacity than GM-CSF (Fig. 3B). Further studies also showed that flagellin upregulated G-CSF, but had no effect on GM-CSF expression in MDSCs (Supplemental Fig. 2A and data not shown). *P. aeruginosa*–induced MDSC generation was significantly reduced using a flagellin-deficient *P. aeruginosa* strain (Fig. 3C). Because flagellin acts mainly through TLR5, we analyzed TLR5 surface expression on MDSCs and found that both in vitro–generated and *P. aeruginosa* CF patient in vivo/ex vivo isolated MDSCs expressed TLR5 (Fig. 3D). To assess the effect of the CFTR in MDSC generation, we used a small-molecule CFTR inhibitor. These studies demonstrated that CFTR inhibition slightly increased the generation of MDSCs but had no significant effect on flagellin-induced MDSC generation (Fig. 3E). These findings were not due to toxic or proapoptotic effects of the CFTR inhibitor and could be reproduced using a second different CFTR inhibitor (Fig. 3E).

Next, we characterized the immunological phenotype of *P. aeruginosa*– and flagellin-induced MDSCs compared with canonical GM-CSF–induced MDSCs. These studies demonstrated that both flagellated *P. aeruginosa* bacteria and purified flagellin protein upregulated surface expression levels of the homeostatic chemokine receptor and HIV coreceptor CXCR4 on MDSCs, whereas GM-CSF treatment had no significant effect on the expression of these surface proteins (Fig. 4). When viewed in combination, these studies indicate that flagellated *P. aeruginosa* strains and purified flagellin protein potently induce MDSCs with a distinct CXCR4high MDSC phenotype.

Flagellin–induced MDSCs functionally suppress T cell proliferation ex vivo and in vitro

To assess the functional capacities of flagellated *P. aeruginosa*–induced phenotypic MDSCs and to corroborate their role as a T cell suppressive cell type, we isolated MDSCs from *P. aeruginosa*–infected CF patients, using gradient centrifugation and sequential magnetic bead isolation, and studied MDSC–T cell interactions ex vivo. These studies using T cell CFSE labeling demonstrated that *P. aeruginosa*–infected CF patient–derived MDSCs efficiently suppressed polyclonal T cell proliferation of both CD4+ and CD8+ T cell subsets in a dose-dependent fashion (Fig. 5A, Supplemental Fig. 2B). As flagellin induced CXCR4high MDSCs, we investigated whether inhibiting CXCR4 functionality using the small-molecule inhibitor AMD3100 has an effect on MDSC-mediated T cell suppression. These studies showed that CXCR4 inhibition had no effect on MDSC–mediated T cell suppression (Supplemental Fig. 2C).

Because IL-17–producing T cells have been previously described as playing a pivotal role in the pathogenesis of chronic infective CF lung disease, we investigated whether CF-isolated MDSCs are capable of modulating IL-17 protein production by CD4+ T cells. These studies demonstrated that MDSCs derived from *P. aeruginosa*–infected CF patients substantially dampened released IL-17 protein (64% reduction of IL-17 protein) (Fig. 5B). These findings on IL-17 cytokine production, quantified in cell culture supernatants, were confirmed by intracellular flow cytometry stainings, showing that MDSCs suppressed IL-17 protein expression in T cells (Supplemental Fig. 2D). In addition to IL-17, MDSCs had an effect on several other cytokines, chemokines, and growth factors, as analyzed by a high-throughput bioplex array (Supplemental Fig. 3).

Finally, we investigated whether *P. aeruginosa*– or flagellin–induced MDSCs feature a similar T cell–suppressive phenotype. These studies showed that flagellated *P. aeruginosa*–or purified flagellin–induced MDSCs mimicked the T cell–suppressive characteristics of CF patient ex vivo–isolated MDSCs in potentially suppressing both CD4 and CD8 T cell proliferation (Fig. 6). When viewed in combination, these studies demonstrate that both ex vivo CF patient–isolated and in vitro *P. aeruginosa*–flagellin–induced MDSCs suppress CD4+ and CD8+ T cell proliferation and modulate Th17 responses.

**Discussion**

*P. aeruginosa* survives in immunocompromised individuals and patients with chronic pulmonary diseases, such as CF, owing to the inability of the host to clear this pathogen efficiently. However, the underlying immune mechanisms remain poorly understood (6). This study reveals a novel mechanism by which flagellated *P. aeruginosa* bacteria subvert the host defense by inducing T cell–suppressive MDSCs. MDSCs could therefore represent a novel therapeutic target in CF and other diseases characterized by infections with *P. aeruginosa* or other flagellated bacteria.

MDSCs represent an innate immune cell subset that efficiently controls adaptive T cell inflammation (9, 10). Our studies provide evidence that granulocytic/neutrophilic MDSCs, regularly absent or only marginally present in healthy control individuals, accumulate in *P. aeruginosa*–infected CF patients. We further show that flagellated *P. aeruginosa* bacteria or the purified TLR5 ligand flagellin potently induces T cell–suppressive MDSCs and upregulates MDSC induction and CFTR. MDSCs were generated in vitro by incubating isolated PBMCs with purified flagellin (10 ng/ml), with or without pretreatment of PBMCs with two different small-molecule CFTR inhibitors (CFTRinh-172, 10μM; GlyH-101, 10μM). For all assays, at least three independent experiments were performed. *p < 0.05. ns, Not significant.
CXCR4 on MDSCs. Importantly, flagellin-deficient *P. aeruginosa* bacteria were significantly impaired in inducing MDSCs, supporting the idea that the effect of *P. aeruginosa* in vivo and in vitro is mainly mediated through flagellin. The significance of the flagellin–TLR5 axis in *P. aeruginosa*–host interactions has been previously demonstrated in numerous studies, including experimental infection models using epithelial cells (1, 2, 5, 17, 19, 20), macrophages (21), neutrophils (18), or in vivo infection strategies (3, 22, 23). Our study thereby confirms and extends the concept that flagellin acts as a key player in shaping the innate but also the adaptive immune response to *P. aeruginosa* in CF lung disease and beyond.

On the basis of our findings, we speculate that flagellin-induced MDSC accumulation in chronic *P. aeruginosa* infection in CF patients has functional immunological relevance, as ex vivo and in vitro *P. aeruginosa*–induced MDSCs significantly suppressed both CD4 and CD8 T cell proliferation and dampened Th17 cell responses, which play a vital role in CF lung disease (24–31). Consequently, MDSCs, as key interface cells between innate and adaptive immunity, may represent a novel therapeutic target in CF patients with functional immunological relevance, as ex vivo and in vitro *P. aeruginosa*–induced MDSCs significantly suppressed both CD4 and CD8 T cell proliferation and dampened Th17 cell responses, which play a vital role in CF lung disease (24–31).

**FIGURE 5.** T cell suppression by CF MDSCs. (A) The suppressive effect of CD66b+–MACS-isolated CF MDSCs was analyzed on CD4+ and CD8+ T cell subsets, using the CFSE polyclonal proliferation assay. (B) The effect of CD66b+–MACS-isolated CF MDSCs on IL-17 secretion by CD4+ T cells (Th17 cells) was analyzed.

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Combining these views and our data on MDSCs into one unifying pathophysiological scenario, we propose the following regulatory loop: 1) *P. aeruginosa* induces MDSCs through a flagellin-mediated mechanism; 2) MDSCs dampen T cell proliferation and Th17 cell responses and thereby protect *P. aeruginosa* from T cell–mediated host defense; and 3) MDSCs downregulate neutrophil recruitment by inhibiting IL-17 release, thereby preventing tissue damage by the unbalanced release of neutrophil-derived proteases and oxidants (47). On the basis of our unexpected observation that an increase of MDSCs correlated with improved pulmonary function in *P. aeruginosa*–infected CF patients, we speculate that the MDSC-mediated downregulation of Th17 responses dampens neutrophilic lung tissue damage and could therefore beneficially modulate the course of CF lung disease, a conception necessitating future investigations. This “anti-inflammatory” action of MDSCs could be of major relevance for progressive stages of CF lung disease, when damage-associated molecular patterns, neutrophil-derived proteases, and protease-generated extracellular breakdown products, such as proline-glycine-proline, further sustain the neutrophil influx and perpetuate IL-17–driven inflammation (48, 49). As 1) *P. aeruginosa*–uninfected CF patients showed increased MDSCs compared with healthy controls, 2) CFTR inhibition had a slight effect on MDSC induction, and 3) flagellin induced host-derived G-CSF expression in vitro, the CFTR mutation itself and non-*P. aeruginosa* host-derived factors probably also contribute to MDSC induction in the course of CF lung disease.

This study demonstrates that flagellin potently induces MDSC generation and that this PAMP mediates the effects of the CF-associated pathogen *P. aeruginosa* on MDSC generation. In chronic CF lung disease, *P. aeruginosa* becomes mucoid, thereby preventing flagellin-host cell interactions. Because our CF patient cohort was characterized by a clear predominance of nonmucoid *P. aeruginosa* isolates and MDSCs tended to be higher in CF patients featuring nonmucoid than mucoid *P. aeruginosa* isolates, we speculate that *P. aeruginosa*–derived flagellin plays an essential role in MDSC induction, at least in pediatric CF cohorts. However, future studies in adult CF patients with a higher proportion of mucoid *P. aeruginosa* phenotypes, using methods such as the swimming motility assays (5), are required to assess whether motile *P. aeruginosa* and functional flagella are required to induce MDSCs in CF in vivo. Moreover, representative longitudinal studies should address the question whether MDSCs can be predictive for the course of CF lung disease, such as disease exacerbations.

When viewed in combination, this study demonstrates that *P. aeruginosa* infection induces MDSCs and subverts T cell immunity, mediated through a novel flagellin-dependent immune mechanism. MDSCs may therefore represent a hitherto unappreciated therapeutic target to modulate inflammation and host defense in CF and other diseases characterized by *P. aeruginosa* infection, such as chronic obstructive pulmonary disease, ventilator-associated pneumonia, wound infections, or primary ciliary dyskinesia, in which we also observed increased MDSCs (N. Rieber and D. Hartl, unpublished observations). Beyond *P. aeruginosa*, these findings may have a broader relevance for infections with flagellated bacteria in general, such as *Helicobacter pylori*, *Salmonella typhimurium*, or flagellated *Escherichia coli* strains. The flagellin-induced upregulation of the G-protein–coupled receptor CXCR4 on MDSCs could pave the way to target this leukocyte subset pharmacologically, using small-molecule inhibitors and underpins, with CXCR4 as HIV coreceptor, a potential role for MDSCs in HIV infection (50). Our observation that flagellin-induced CXCR4high MDSCs, but that CXCR4 was dispensable for MDSC-mediated T cell suppression, may further suggest that CXCR4 in this setting may play a role in MDSC functionality beyond T cell suppression, such as MDSC migration, homing, or survival. Because signal transducer and activator of transcription 3 (STAT3), S100 proteins, and NO have been previously implicated in the generation and functionality of MDSCs (10), interfering
with these pathways might represent a future therapeutic strategy in CF lung disease and other pathological conditions associated with flagellated bacteria.

Disclosures

The authors have no financial conflicts of interest.

References


