Tumor Necrosis Factor–α–Converting Enzyme: Its Role in Community-Acquired Pneumonia

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Bronchoalveolar lavage fluid recovered from infected and uninvolved lungs of patients with community-acquired pneumonia (CAP; n = 16) on day 6 ± 0.8 was analyzed for cytokine, soluble receptor, and antagonist levels. The role of tumor necrosis factor (TNF–α–converting enzyme (TACE)) in the resolution of the local inflammatory response was investigated. TNF–α, interleukin (IL)–1β, and IL–6 were elevated in the infected versus uninvolved lobe, whereas IL–10 was not. Epithelial lining fluid (ELF) cytokine levels correlated with intracellular cytokine expression. Levels of proTNF–α were reciprocally related to TNF–α ELF levels. Levels of soluble receptors, generated by TACE cleavage of membrane-bound precursors, were compartmentalized to infected ELF. TACE was down-regulated by internalization in cells from the site of infection. These data demonstrate that, in vivo during CAP, TACE has a role in regulating resolution of the local inflammatory response by modulating levels of pro- and counterinflammatory mediators.

Community-acquired pneumonia (CAP) is a common condition characterized by a high burden of morbidity and mortality. CAP rates among the 6 most common causes of death in the United States, where 2–3 million cases occur annually. The percentage of mortality among hospitalized patients ranges from 2% to 30% but is <1% for patients not requiring hospitalization [1–5]. The critical factors responsible for immunoregulation in the lung and the variation in response and outcome among different patients require a balance between endogenously generated pro- and anti-inflammatory mediators.

Among the most important proinflammatory mediators in CAP are tumor necrosis factor (TNF–α), interleukin (IL)–1β, and IL–6 [6–9], whereas IL–10 has been suggested to be critical in counterbalancing their effects and achieving adequate resolution of the septic process [10]. TNF–α is produced as a 26-kDa membrane-associated protein (proTNF–α), which is cleaved enzymatically by TNF–α–converting enzyme (TACE) into a soluble 17.5-kDa cytokine [11]. It is a pleiotropic early response proinflammatory cytokine capable of inducing IL-1β and IL-6. Elevated TNF–α levels in bronchoalveolar lavage (BAL) fluid are associated with CAP [9] and have been implicated as a potential marker of severity of pneumonia. Similarly, both IL-1β and IL-6 have been reported to be associated with CAP and also are present at elevated levels in CAP BAL fluid [6, 9].

The inflammatory response to pulmonary infection is ideally compartmentally restricted to the infected lung parenchyma [9, 12, 13] and subsequently resolved without damage to the host. Resolution of the inflammatory process is regulated by counterinflammatory cytokines and cytokine antagonists. IL–10 is the principal cytokine that regulates this process; however, soluble cytokine receptors that act as specific cytokine antagonists also have important roles in modulation of inflammation [14].

TACE may have a role in the regulation of sepsis and may be a potentially important regulator of pulmonary inflammation in CAP, particularly during the resolving phase. This multifunctional protein, in addition to regulating soluble TNF–α levels [13], also has been shown recently to mediate shedding of L-selectin from the surface of leukocytes, an important event during leukocyte migration from the circulation to sites of inflammation [15]. TACE also cleaves the ectodomains of transforming growth factor–α, CD30, TNF-related activation-induced cytokine, growth hormone receptor, macrophage–colony stimulating factor receptor, fractalkine, neuregulins, and heregulin family members from cell surfaces [15–22] and participates in α-secretase cleavage of amyloid precursor protein [23]. Of particular interest with respect to regulation of inflammation in CAP is the fact that TACE generates soluble TNF receptors I and II (sTNFRI/II), soluble IL–1RII (sIL–1RII), and soluble IL–6R (sIL–6R) from their cognate membrane-bound precursors [15, 24, 25]. These are direct antagonists of TNF–α and IL–1β, respectively. The IL-6 receptor also is a substrate for
TACE [25]. sIL-6R generated by TACE cleavage can associate with IL-6 and enhance its biological activity [26]. Recently, it has emerged that IL-6/sIL-6R complexes have a role in modulating leukocyte recruitment during acute inflammation by suppressing neutrophil recruitment and attracting mononuclear leukocytes [27]. This is an important process in the resolution of inflammation.

In the present study, we have characterized pro- and anti-inflammatory cytokine expression in unilateral CAP and demonstrate that the proinflammatory cytokines TNF-α, IL-1β, and IL-6 and their cognate antagonists sTNFRI/II, sIL-1RII, and sIL-6R, respectively, are compartmentally restricted to the site of infection during resolution of CAP. The data show that cytokine epithelial lining fluid (ELF) levels correlate with local cytokine production by ELF cells, and that TNF-α ELF levels are reciprocally related to levels of proTNF-α expressed on ELF cells. The data implicates TACE in regulation of the inflammatory response in CAP by generating soluble TNF-α and, furthermore, supports a role for TACE in regulation of the inflammatory immune response in CAP, by the generation of cytokine-specific antagonists.

Materials and Methods

Study population. Sixteen patients (7 men and 9 women; mean age ± SE, 55 ± 3.7 years) were diagnosed with a new infiltrate on chest radiograph, and findings were consistent with consolidation and at least 2 of the following features: new cough and/or sputum production, fever, hypothermia, rigors, sweats, change in sputum color, chest discomfort, pleuritic pain, dyspnea, fatigue, or myalgia. Exclusion criteria included hospitalization/residential care for >48 h before onset of symptoms, immunocompromised hosts, human immunodeficiency virus (HIV) infection, tuberculosis, aspiration, lung cancer, drug addiction, alcohol abuse, prior chemotherapy, or allergic bronchopulmonary aspergillosis. All patients had unilateral CAP, with all but one being unilateral (which was bilobar). There were 9 smokers, 4 ex-smokers, and 3 nonsmokers. The Pneumonia Patient Outcomes Research Team prediction rule score for risk class was calculated [28]. All patients scored >90 and were ranked as class IV or V. Patients were subdivided according to whether they fulfilled the standard criteria for the systemic inflammatory immune response syndrome (SIRS). Having ranked patients non-SIRS-SIRS4, the group had a mean score of SIRS2 [29]. After informed consent was obtained, under a protocol approved by Beaumont Hospital Ethics Review Board, BAL fluid was recovered (6 ± 0.8 days from time of presentation) from infected and contralateral uninvolved lungs [30]. All BAL samples were negative, as determined by quantitative culture using a threshold of 104 cfu/mL. Sputum and blood Gram’s stain and culture were performed. Similar to other studies, Streptococcus pneumoniae was identified in 44% patients [31]. Three patients had pneumonia and IL-6 after their initial course of therapy, which was according to the American Thoracic Society 1993 guidelines [32]. Eighteen age-matched healthy control subjects also were studied (11 men and 7 women; mean age ± SE, 55 ± 4.2 years). ELF volumes were quantified (0.7 ± 0.16, 0.7 ± 0.12, and 0.9 ± 0.12 mL for uninvolved, infected, and control subjects, respectively) [33].

ELF cytokine/antagonist levels and molar ratios. Total antigenic concentrations of IL-1β, IL-6, TNF-α, IL-10, and IL-13 in ELF were measured by ELISA (R&D Systems) with detection sensitivities of 3.9, 0.6, 4.4, and 3.9 pg/mL and 6 ng/mL, respectively. Soluble cytokine receptors and IL-1 receptor antagonist (IL-1ra) were measured by ELISA: sTNFRI and II (BioSource) and IL-1ra, sIL-1RII, and sIL-6R (R&D Systems), with detection sensitivities of 50 ng/mL and 100, 14, 10, and 1.5 pg/mL, respectively. Cytokine:antagonist(s) molar ratios were calculated.

TNF-α bioassay. TNF-α bioactivity was measured by induced cytotoxicity of L929 cells [34]. L929 cells (ECACC) were plated in 100 µL Dulbecco’s modified Eagle’s medium supplemented with 2% fetal calf serum (Life Technologies) at 3.5 × 10⁴/well in a 96-well plate. After 24 h, 50 µL of 4 µg/mL actinomycin D (Sigma) and different concentrations of TNF-α (0.125–2000 pg/mL) or ELF volumes containing 20 pg/mL (equivalent to the IC₅₀ of TNF-α) were added to each well. After 24 h, 10 µL 3,4,5-trimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Sigma; 5 mg/mL in PBS [pH 7.2]) was added to each well for 4 h. After the addition of 50 µL/well lysing solution (20% SDS/50% N,N-dimethylformamide), the absorbance of each well was measured at 570 nm. Cytotoxicity by MTT conversion at each concentration of TNF-α was compared with untreated (control) cells (100% survival).

Membrane-bound and intracellular cytokines and TACE. For cell-surface antigen staining, Fc-blocked cytopsins, were labeled with anti-human proTNF-α-fluorescein isothiocyanate (FITC; FITC; R&D Systems) or with anti-human TACE antibody (huTACE M220; Immunix) and FITC-labeled anti-mouse F(ab), (DAKO). Intracellular (ic) levels of TACE, IL-6, and IL-10 were quantified in permeabilized cytopsins using huTACE M220, anti-human IL-6–FITC, and IL-10–phycoerythrin (PE; BioSource). Isotype control slides were prepared. Cytopsins were counterstained with propidium iodide (Pl Molecular Probes).

Laser scanning cytometry (LSC). LSC (Compucyte) was used to quantify membrane-bound and intracellular cytokine and TACE expression. FITC, PE, and PI cellular fluorescence of at least 5 × 10⁴ cells were measured by separate photomultipliers at 530 ± 20, >560, and >610 nm, respectively. The threshold contour was set on red fluorescence to detect all PI-stained nuclei. Artificially contoured debris was gated out on the basis of contour size. Aggregated cells were gated out using an algorithm in the LSC software that finds and marks multiple cells. Individual proTNF-α–, TACE–, IL-6– or IL-10–positive cells were identified and quantified using Compucyte software on the basis of integrated green (proTNF-α, TACE, and IL-6) or orange (IL-10) fluorescence [35, 36].

The anti–proTNF-α–FITC antibody recognizes both proTNF-α and TNF-α bound to its receptor on the cell surface. To distinguish these 2 types of antibody binding, cells were labeled, and antibody binding was quantified by LSC. Cells then were washed in a low-pH glycine buffer (0.05 M glycine and 0.15 M NaCl [pH 3]) [37], and antibody binding was measured again.

Statistical analysis. Data were analyzed using GraphPad Prism 3.0 (GraphPad Software). Results are expressed as mean ± SE and
were compared by Wilcoxon matched-pairs test or Mann-Whitney U test, as appropriate.

Results

Cell Differentials in Infected and Uninvolved ELF

Cytospin preparations were analyzed to determine cell numbers per milliliter of BAL fluid and cell populations present in ELF. Samples from the infected lung contained elevated numbers of cells ($15.7 \times 10^6 \pm 1.4 \times 10^6$ cells/mL), compared with those of uninvolved samples ($1.55 \times 10^6 \pm 0.8 \times 10^6$ cells/mL). The macrophage:neutrophil ratio in uninvolved ELF was 20:1, compared with 2:1 for infected ELF. Although the absolute number of macrophages present in infected ELF was higher than that for the uninvolved lung ($9.9 \times 10^6 \pm 8.9 \times 10^6$ cells/mL vs. $1.6 \times 10^6 \pm 0.7 \times 10^6$ cells/mL), this was not significant. CAP was characterized by neutrophil influx, with 76-fold more neutrophils at the infection site ($7.8 \times 10^6 \pm 3.8 \times 10^6$ cells/mL and $5.9 \times 10^6 \pm 5.2 \times 10^6$ cells/mL; $P < .0001$, Wilcoxon matched-pairs test, for uninvolved vs. infected, respectively).

TNF-α, IL-1β, and IL-6 Production Is Compartmentalized in Unilateral CAP

ELF levels. Levels of the proinflammatory cytokines TNF-α, IL-1β, and IL-6 and the counterinflammatory cytokines IL-10 and IL-13 were measured in ELF from control subjects and from both the infected and contralateral uninvolved lobes of individuals with CAP by ELISA. TNF-α and IL-1β (uninvolved vs. infected lobes, 61 ± 17 vs. 191 ± 74 pM/ELF [$P = .0051$]; 20 ± 6 vs. 65 ± 24 pM/ELF [$P = .0476$], respectively, Wilcoxon matched-pairs test) were compartmentalized to the site of infection (figure 1A and 1B). Both TNF-α and IL-1β levels in infected ELF also were elevated compared with those in control ELF (86 ± 25 pM/ELF and 19 ± 7 pM/ELF for TNF-α and IL-1β, respectively). IL-6 also was compartmentalized (uninvolved vs. infected lobes, 41 ± 13 pM/ELF vs. 75 ± 20 pM/ELF; $P = .05$, Wilcoxon matched-pairs test) and levels in infected ELF were significantly elevated, compared with levels in control ELF (5 ± 1 pM/ELF; $P = .0113$, Mann-Whitney U test; figure 1C).

The counterinflammatory cytokine IL-10 was not compartmentalized to infected ELF (uninvolved vs. infected lobes, 29 ± 13 vs. 27 ± 10 pM/ELF), but levels were elevated 3-fold, compared with that of control ELF (10 ± 9 pM/ELF; $P = .001$ and $P = .0003$ for uninvolved and infected ELF, respectively; Mann-Whitney U test; figure 1D). IL-13 was not detected in any of the samples.

Intracellular cytokine expression. To confirm whether the intermediate levels of IL-6 detected in uninvolved ELF, compared with that of control or infected ELF, were due to spillover from the infected lobe or due, rather, to in situ cytokine expression by ELF cells, icIL-6 levels were quantified using fluorescence laser-scanning cytometry. Cells from the infected lobes of patients with CAP produced 4-fold more icIL-6 than cells from contralateral uninvolved lobes or those from controls (figure 2A and 2B) or from cells labeled with an appropriate isotype control antibody (data not shown). This indicated that cytokine expression in the uninvolved lobe occurs in situ and is not due to spillover from the infected lobe.

icIL-10 production also was quantified. Cells from the infected and uninvolved lobes expressed similar amounts of icIL-10, as was seen for levels of IL-10 in ELF (figure 2C and 2D). icIL-10 levels were increased 3.4- and 2.5-fold for uninvolved and infected ELF cells, respectively, compared with levels of control cells. An isotype antibody was used as a control (not shown). These data confirm that ELF cytokines are expressed by inflammatory cells in situ in the lung during CAP.

Reciprocal Relationship between proTNF-α and Soluble TNF-α

Soluble TNF-α is generated from membrane-bound proTNF-α by cleavage via TACE [11]. Levels of proTNF-α on cells from infected and uninvolved lobes of individuals with CAP were quantified by fluorescence microscopy. An isotype antibody was used as a control (not shown). Cells from infected ELF expressed 63% ± 10% lower levels of proTNF-α than cells from uninvolved ELF ($P = .002$, Mann-Whitney U test). The levels of proTNF-α correlated reciprocally with TNF-α ELF levels in both infected and uninvolved ELF (figure 3). This data implicates TACE in regulation of the proinflammatory immune response in CAP.
Elevated TACE Activity at Site of Infection

Compartmentalization of cytokine-specific antagonist activity and inhibition of cytokine activity. TNFRI, TNFRII, IL-1RII, and IL-6R are substrates for TACE [15, 24, 25]. Cleavage of these receptors generates soluble antagonists, sTNFRII, sIL-1RII, and sIL-6R, which specifically bind to their cognate cytokines, TNF-α, IL-1β, and IL-6, respectively. Levels of these antagonists were measured in ELF from the infected and contralateral uninvolved lobes of individuals with CAP by ELISA and were found to be compartmentalized to the site of infection (figure 4; involved vs. infected, 1.2 ± 0.1 vs. 8.6 ± 4.3 nM/ELF \( P = .029 \) for sTNFRII; 0.3 ± 0.1 vs. 3.1 ± 1.5 nM/ELF \( P = .0296 \) for sIL-1RII; and 0.3 ± 0.06 vs. 1.1 ± 0.3 nM/ELF \( P = .0209 \) for sIL-6R; all Mann-Whitney \( U \) test). There was no relationship between bacteremia, risk class, or SIRS score and cleavage of TACE substrates. Pneumococcal patients with CAP had elevated proinflammatory cytokine and soluble receptor ELF levels, compared with those of the nonpneumococcal subset, but these differences were not significant. Smokers had elevated levels of sTNFRII and sIL-6R in infected ELF than did nonsmokers (5.8 ± 2.6 vs. 0.9 ± 0.2 nM/ELF \( P = .014 \)) and 0.9 ± 0.4 vs. 0.27 ± 0.1 nM/ELF \( P = .034 \) for smokers and nonsmokers, respectively; Mann-Whitney \( U \) test). TNF-α ELF levels also were elevated in smokers than in nonsmokers (not shown). Levels of IL-1ra, a naturally occurring inhibitor of IL-1β [38] that is not generated via TACE cleavage, were elevated in infected versus uninvolved ELF (7.1 ± 7 vs. 3.7 ± 1.4 nM/ELF); however, this was not statistically significant.

Cytokine:antagonist molar ratios were calculated for TNF-α and IL-1β. These were 1:20 versus 1:45 (uninvolved vs. infected) for TNF-α:sTNFRII. TNF-α bioactivity also was measured in infected ELF samples. TNF-α–induced cytotoxicity of L929 cells could not be induced by volumes of infected ELF containing 20 pg/mL of TNF-α, a concentration equivalent to the IC\(_50\) of recombinant TNF-α. Three infected samples had detectable TNF-α activity; however, these were impaired by up to 50%, which indicates that TNF-α activity was neutralized in infected ELF. Cytokine:antagonist molar ratios for IL-1β:IL-1ra plus sIL-1RII were 1:355 versus 1:106 for uninvolved versus infected, which indicates that IL-1β antagonists were present in molar excess, compared with that of their cognate cytokines, in both uninvolved and infected ELF. sIL-6R can potentiate IL-6 activity [26]. For this reason, the calculation of relative IL-6 activity is not appropriate.

In Vivo Down-Regulation of TACE

TACE expression on cells from infected and uninvolved lobes was quantified by fluorescence cytometry. Cells from infected ELF expressed 43% ± 18% lower levels of surface-expressed TACE than cells from uninvolved ELF (\( P = .0214 \), Mann-Whitney \( U \) test; figure 5A). A representative histogram shows the more intense fluorescence from uninvolved than from infected cells (figure 5B).

After cleavage of its substrates, TACE is down-regulated by internalization [39]. We examined whether this occurs in vivo in cells from infected ELF by quantifying anti-TACE antibody staining on fixed versus fixed and permeabilized cells. Figure 5C...
Figure 4. Compartmentalized expression of tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6 soluble (s) receptors (R). Levels of sTNFRI, sTNFRII, sIL-1RII, and sIL-6R in uninvolved (white bars) and infected (black bars) epithelial lining fluid (ELF) were measured by colorimetric ELISA using monoclonal antibody pairs (n = 16). Levels are expressed as nM/ELF (*P < .05, Wilcoxon matched-pairs test).

and 5D show that TACE is internalized in cells isolated from infected ELF, with total TACE expression >4-fold elevated versus cell surface–expressed TACE (P = .0313, Wilcoxon matched-pairs test).

Discussion

Inflammation in the lungs of patients with unilateral CAP reflects a balance between proinflammatory cytokines and mediators with anti-inflammatory effects. In this study, we have demonstrated that the proinflammatory cytokines TNF-α, IL-1β, and IL-6 are compartmentalized to the site of infection; however, compartmentalized production of specific antagonists with counterinflammatory properties also is elevated. Our study describes a role for TACE in the regulation of these events.

Ideally, the inflammatory response in unilateral CAP is compartmentalized [9, 12, 13], which implies the presence of regulatory mechanisms directed at containing inflammation and preventing development of overt systemic inflammation culminating in severe sepsis. In another study, TNF-α, IL-1β, and IL-6 have been shown to be present at elevated levels in infected ELF versus uninvolved ELF in a cohort of patients with CAP [9], and our data support this. In the present study, we also quantified levels of the TACE-generated cytokine-specific antagonists sTNFRI/II and sIL-1RII and found that these factors also were compartmentalized to the infection site and (with IL-1ra) were present at sufficient molar concentrations to inhibit activity of their cognate cytokines. IL-1β binds with high affinity to sIL-1RII and is inhibited by 10–100 molar excess of IL-1ra, as is shown here for both uninvolved and infected lobes [40, 41]. Exaggerated inflammatory responses are associated with low TNF-α/sTNFRI+II ratios [42]; however, this ratio was elevated in infected ELF, and our bioassay analysis confirmed that TNF-α activity was impaired at the site of infection. sIL-6R levels also were compartmentalized and elevated in infected ELF. During inflammation, initial neutrophil infiltration is replaced by a more sustained population of mononuclear cells. IL-6 and sIL-6R have been implicated in controlling this pattern of leukocyte recruitment during inflammation [27]. Neutrophil-derived sIL-6R acts as a regulator of CXC and CC chemokine expression by suppressing neutrophil recruitment and attracting mononuclear cells. This is a key event in resolution of inflammation. Taken together, the findings presented here provide evidence for a role for TACE in regulating the balance between pro- and counterinflammatory mediators in CAP.

The host response to infection is idiosyncratic, in that inflammation is appropriately resolved in some patients whereas, in others, an excessive inflammatory response is associated with a poor clinical outcome. Cell-surface expression of TNFRI/II, IL-6R, and IL-1RII can be up-regulated by a variety of different stimuli that induce macrophage maturation [43–45]. Our data demonstrated elevated levels of TACE-generated products in the infected ELF of smokers versus nonsmokers, which suggests that TACE activity may be modulated by cigarette smoke. Conversely, it is possible that, under circumstances of aberrant receptor expression or inhibition of TACE activity, an exci-

Figure 5. Tumor necrosis factor (TNF)-α-converting enzyme (TACE) is down-regulated and internalized at the site of infection in unilateral community-acquired pneumonia. A. Cell-surface TACE expression on cells from uninfected (U, white bar) and infected (I, black bar) epithelial lining fluid (ELF) was quantified by laser scanning cytometry (*P < .05, Wilcoxon matched-pairs test; n = 8). B. A representative histogram of cell-surface TACE expression on cells from uninvolved (open) and infected (closed) ELF. C. Cell-surface (s, white bar) and total (s+ic, black bar) TACE expression on cells from infected ELF was quantified by laser scanning cytometry (*P < .05, Wilcoxon matched-pairs test; n = 4). D. A representative histogram of cells from infected ELF analyzed for cell surface (clear) and both surface and intracellular (solid) TACE expression by laser-scanning cytometry.
erbated inflammatory response might occur, such as is seen with the subpopulation of patients with CAP who develop sepsis. Inhibiting IL-1 or TNF alone in sepsis has not yielded success in clinical trials; however, combination immunotherapy with IL-1ra and sTNFR has been shown to decrease sepsis mortality in an animal model [46]. This demonstrated that strategies directed against both TNF and IL-1 can be effective therapeutically. TACE may fulfill this role in vivo by generating factors with anti-TNF and anti–IL-1 activity.

In addition to soluble receptors, the counterinflammatory cytokine IL-10 can play an important role in decreasing the inflammatory response in CAP. IL-10 counteracts a number of the biological effects of proinflammatory cytokines by enhancing resolution of pulmonary inflammation in vivo by promoting apoptosis of neutrophils and by inhibiting proinflammatory cytokine expression [47, 48]. Our data show that IL-10 levels were not compartmentalized but that cells from both the infected and uninvolved lungs expressed IL-10. This was a surprising observation and is at variance with the findings in previous animal models of pneumonia. Intranasal inoculation with S. pneumoniae in normal mice results in a marked increase in IL-10 concentrations in their lungs [49]. IL-10 is largely compartmentalized and is barely detectable in plasma. It is possible that some systemic factor may be stimulating production of IL-10 but not the other cytokines. IL-13 is a Th2 cytokine that has a principle role in allergy and asthma. We measured IL-13 in our BAL samples to determine whether IL-13 may have an anti-inflammatory role in CAP, given that it can suppress the cytotoxic function of macrophages and the production of some proinflammatory cytokines. The detection limit of the ELISA we used to measure IL-13 was 6 ng/mL, yet, even using the equivalent of 1 mL BAL fluid concentrated by ultrafiltration, we were unable to detect any IL-13 in our BAL samples, which suggests that this cytokine is not important during unilateral CAP.

Neutrophil-dominated airway inflammation is associated with elevated levels of the neutrophil proteases neutrophil elastase, cathepsin G, and proteinase 3. Neutrophils accounted for almost 40% cells in infected ELF in our patients. TACE-independent release of TNF-α has been reported in vitro in the presence of activated neutrophils or purified proteinase 3 [50]. Therefore, it is possible that proteolytic events other than those mediated by TACE may be responsible for generating some of the soluble factors studied here.

The identification of TACE as the factor responsible for generating soluble TNF-α initially highlighted its importance as an inflammatory regulator. A number of recent studies have implicated TACE in the regulation of many other biological processes, with the discovery that its substrate specificity extents to cytokine receptors, adhesion molecules, and growth factors [11, 15–25]. Although the complete repertoire of TACE substrates remains to be elucidated, it is clear that TACE represents an important regulator of inflammatory events.

It remains to be shown whether TACE represents a marker of inflammation for CAP; however, this is unlikely, given that TACE is ubiquitously expressed and attempts to up-regulate its expression have proved unsuccessful [11]. Moreover, because TACE becomes down-regulated after cleavage of its substrates [36], its usefulness as a prognostic determinant in CAP seems limited. What is evident from our studies on ELF cells from both infected and uninvolved lungs of patients with CAP is that down-regulation of TACE does occur in vivo during acute pulmonary inflammation.

CAP remains one of the most significant causes of morbidity and mortality in both the developed and developing worlds. It is a significant cause of death not only in otherwise healthy individuals but also in patients with other comorbid illnesses. TACE has an integral role in modulation of inflammation in CAP. TACE agonists or therapeutic TACE proteins may represent useful options for the management and control of sepsis associated with CAP.

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References

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