At early stage of cystic fibrosis (CF), patient lungs are mainly colonized by Staphylococcus aureus (SA) while Pseudomonas aeruginosa (PA) becomes predominant at late stage. Type IIA secretory phospholipase A2 (sPLA2-IIA) is a bactericidal enzyme produced by mammalian cells. We show here that this enzyme kills laboratory and clinical strains of SA with an EC 50 at 10 ng/ml but had no effect on PA strains even at concentrations above 10 µg/ml. This killing is due to selective hydrolysis by sPLA2-IIA of phosphatidylglycerol, the major membrane lipid of SA. Transgenic mice over-expressing human sPLA2-IIA are protected from SA, but not PA lung infection. In lung co-infection animal models, SA is eradicated faster than PA that enhances SA clearance. This clearance is abolished by pharmacological inhibition of PLA2-IIA. PA but not SA induces sPLA2-IIA expression in human bronchial CF epithelial cells IB3 and alveolar macrophages (AMs) by different mechanisms. In AMs, PA induces sPLA2-IIA via LPS/TLR4/NF-κB pathway. In IB3, this induction occurs via the type-III secretion system. Among the proteins of this system ExoS toxin plays the major role in sPLA2-IIA induction. The transcription factor KLF seems to play a key role in ExoS-induced sPLA2-IIA expression in IB3 cells. Expectorations from adult CF patients exhibit high levels of sPLA2-IIA that play a major role in the killing of SA, but not PA, by these expectorations. Our results suggest that PA-induced sPLA2-IIA expression plays a role in the elimination of SA from CF lung. This highlights a new mechanism by which a pathogen can eliminate another pathogen by using the innate immunity of the host.