MRSA-Induced Endothelial Injury and Lung Injury Are Reversed by FTY720 S-Phosphonate

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Rationale: Effective therapies are needed to preserve the lung vascular barrier that is disrupted during the Acute Respiratory Distress Syndrome (ARDS). Prior work has suggested that FTY720 S-phosphonate (Tys), an analog of the endogenous phospholipid sphingosine 1-phosphate (S1P) and the pharmaceutical compound FTY720, has potential to protect against endothelial barrier disruption in vitro and in vivo. An important mechanism by which Tys decreases permeability is by preserving expression of the barrier promoting S1P receptor 1 (S1PR1). In this study we characterized the potential of Tys to protect against lung vascular injury induced by the ARDS stimulus methicillin-resistant Staph aureus bacteria (MRSA). Methods: Human pulmonary artery or microvascular endothelial cells (EC) were used for in vitro experiments. Immunoprecipitation, CHIP, ELISA, immunofluorescence microscopy and western blotting were performed per standard protocols. Heat-killed MRSA (HK-MRSA) was used in vitro, and intratracheal (IT) live MRSA was used in mice to induce lung injury in vivo. Results: HK-MRSA caused Rho activation, MLC phosphorylation, stress fiber formation, peripheral VE-cadherin loss, NF-κB phosphorylation, IL-6 and IL-8 release, and increased permeability in cultured human lung EC. All of these effects were inhibited by Tys (1 µM). HK-MRSA also induced epigenetic changes in lung EC, including methylation of histone H3 lysine 4. By chromatin immunoprecipitation (CHIP) analysis, HK-MRSA significantly enriched H3K9Ac in the NFAT binding region of the S1PR1 promoter. These epigenetic effects were inhibited by Tys treatment. In vivo, IT MRSA in mice causes a significant increase in BAL protein and total cell count levels compared to PBS (18 hours). Pretreatment or post-treatment with Tys significantly reduced BAL protein levels and BAL total cell count after MRSA compared to the vehicle control group. Compared to other potent S1PR1 agonists, RP001 or CYM5442, Tys exhibited prolonged barrier promotion in vitro and did not induce ubiquitination and degradation of S1PR1. Conclusion: Tys reverses many of the injurious effects of MRSA on lung EC in vitro and mice in vivo. These results suggest that S1PR1 agonists such as Tys may have potential utility in ARDS.

This abstract is funded by: NHLBI P01 HL126609

Am J Respir Crit Care Med 2020;201:A7845
Internet address: www.atsjournals.org