Identification of Compounds that Inhibit the Binding of the FtsZ-Targeting Antibacterial Agent TXA6101 to Serum Albumin

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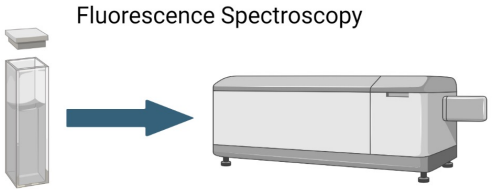
Methicillin-resistant Staphylococcus aureus (MRSA) infections are a global public health problem. TXA6101 is a potent inhibitor of the FtsZ protein that in turn disrupts bacterial cell division. However, TXA6101 activity against MRSA decreases in the presence of serum albumin. The purpose of this study is to identify inhibitors of TXA6101 binding to albumin with the potential of enhancing activity against MRSA when used in combination with TXA6101. To this end, fluorescence spectroscopy was used to characterize TXA6101 binding to human and mouse serum albumin (HSA and MSA, respectively) at 37°C. Assays where TXA6101 was titrated into 1.8 µM albumin revealed TXA6101 bound tightly to HSA (Kd = 3.67 µM) and MSA (Kd = 0.89 µM). TXA6101 binding to both HSA and MSA was accompanied by reduction in a fluorescence peak at 340 nm corresponding to the tryptophan residue in site 1 of albumin, and induction of a peak at 430 nm corresponding to albumin-bound TXA6101. Further fluorometric studies probed the impact of two potential albumin binding inhibitors (indomethacin or iopanoic acid) on the binding of TXA6101 to HSA. These studies revealed that both compounds inhibited TXA6101 binding, with the reduction being greater for indomethacin. Future studies will be aimed at determining whether TXA6101 combined with indomethacin or iopanoic acid can potentiate activity against MRSA in the presence of HSA or MSA in culture, and ultimately in vivo. Supported by the NIH grants R25ES020721 and RO1AI118874, and the American Society for Pharmacology and Experimental Therapeutics SURF Program.

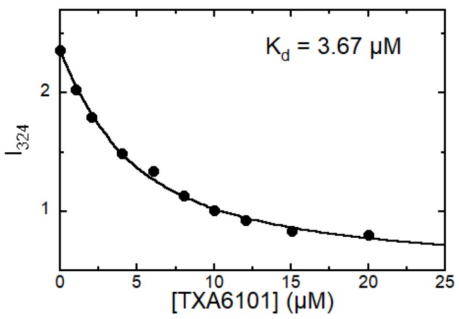
Methods



- TXA6101 binding to serum albumin
- Impact of different inhibitors on TXA6101 binding to serum albumin

Results

Binding Curve for the Interaction of TXA6101 with Human Serum Albumin (HSA)



Impact of Indomethacin on TXA6101 Binding to HSA