The role of an uncharacterized family of α/β-hydrolases in the antimicrobial resistance

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Current antimicrobial resistance (AMR) surveillance systems are incomplete and often overlook critical antimicrobial resistance genes (ARGs) in environmental and animal reservoirs. Identifying these gaps is essential to improving AMR surveillance, stewardship programs, and clinical practices. During recent AMR surveillance efforts, we functionally annotated a member of the α/β-hydrolase superfamily as a macrolide esterase. This enzyme, which we named EstT, inactivates tylosin and related macrolide antibiotics, making it the founding member of a previously unrecognized group of AMR determinants. EstT has numerous homologs within the α/β-hydrolase superfamily, exhibiting various sequence identities. This suggests the existence of many α/β-hydrolases that may contribute to macrolide inactivation. Our findings underscore the need for further studies on the α/β-hydrolase superfamily and its role in macrolide resistance to mitigate the global AMR threat. We continue to identify and characterize the functions and structures of EstT homologs to understand better how these Ser-His-Asp catalytic triad-containing enzymes bind and hydrolyze antibiotics. The activities, substrate specificities, and three-dimensional structures of these serine-dependent macrolide esterases will be discussed in the broader context of antimicrobial use in agriculture.