MS054.O03

Allosteric mechanism in PBP2a controlling resistance of Methicillin-resistant Staphylococcus aureus

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One of the most threatening hospital-associated pathogens is the bacterium Staphylococcus aureus, which currently represents a major problem in both the clinical and community settings globally. Several strains exist that are resistant to a wide range of beta-lactam antibiotics, known as methicillin-resistant S. aureus or MRSA. beta-Lactam antibiotics block the synthesis of the bacterial cell wall through inhibition of the transpeptidase activity of Penicillin-Binding Proteins (PBPs). An essential protein in MRSA resistance is PBP2a. We have reported the crystal structure of PBP2a in complex with ceftaroline [1] one of the few antibiotics available for treatment of infections by MRSA. We identified an allosteric binding site—a remarkable 60 Å distant from the DD-transpeptidase active site— that once occupied, a multiresidue conformational change culminates in the opening of the active site to permit substrate entry. In a series of different investigations [2-4], we have characterized this allosteric mechanism, its implications in clinics and the development of a new family of antibiotics against MRSA. Notwithstanding their weak affinity for the allosteric site, other antibiotics such as oxacillin, cefepime, and ceftazidime are recognized by the allosteric site and able to produce strong and dramatic conformational changes at the active-site region [4]. Thus, reinforcing the role of the allosteric site of PBP2a as the primary site in antibiotics recognition. The discovery of allostery in MRSA remains the only known example of such regulation of cell-wall biosynthesis and represents a new paradigm in fighting MRSA.

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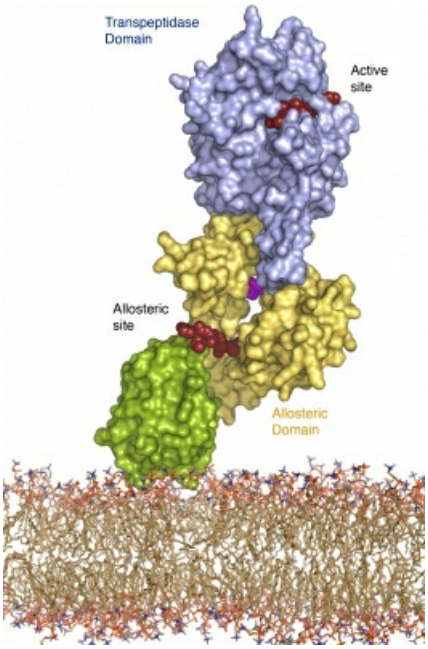

Keywords: MRSA, allostery, PBP2a