Poster Presentation

MS45.P12

Type II topoisomerases as targets for rational drug design

I. Laponogov[1,2], D. Veselkov[1], T. Umrekar[1], I. Crevel[2], X. Pan[2], L. Fisher[2], M. Sanderson[1]

[1]King's College, Randall Division of Cell and Molecular Biophysics, London, UK, [2]St. George's University of London, Division of Biomedical Sciences, London, UK

Bacterial drug resistance is a growing and now widely recognised threat and the limited number of new antibacterials developed in the recent years is a serious matter of concern. One of the approaches to combat this growing threat is to investigate the mechanisms of action of currently available antibacterials, as well as studying the way that bacteria are currently developing drug resistance and may potentially in the future develop drug resistance to known remedies. This knowledge should in turn be used in rational drug design and the general development of the appropriate frameworks for combating bacteria, while at the same time keeping the negative side effects of the drugs to the acceptable minimum. This is especially important when both bacteria and humans share similar drug targets, such as is the case for topoisomerases (in humans, the latter are also targeted by anti-cancer drugs). Our main protein targets of interest are type II topoisomerases which are involved in regulation of the DNA supercoiling in both bacteria and eukaryotes and also in decatenation of bacterial daughter chromosomes during cell division. Type II topoisomerases are performing their biological action by binding the double stranded DNA (called G-segment or Gate-DNA), temporarily cleaving it and passing another double stranded DNA (called T-segment) in the ATP-assisted process via the cleavage region thus changing the linking number in steps of ±2. After that the G-segment is resealed and released. Several drugs were found to be able to disrupt this process ultimately resulting in the cell death (thus having anti-bacterial or anti-cancer action). Here we present our studies of the protein-DNA-drug interactions which are involved in the action of currently clinically used quinolone antibacterials as well as their newly developed alternatives (such as quinazolinediones) in relation to their mechanism of action and already established potential routes for developing drug resistance in bacteria. We present the results for different pathogens (including, but not limited to Streptococcus pneumoniae and Klebsiella pneumoniae) and also compare the configuration of the active site with the one from type II topoisomerases from a human organism.

Keywords: antibiotic resistance, antibacterial agents, protein-dna complex