Keynote

Force spectroscopy of anticancer drugs binding nucleic acids

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The recent advent of micromanipulation tools allow scientists to monitor and follow molecular processes one molecule at a time. By exerting tiny forces (in the range of piconewtons) on individual molecules, single molecule experiments allow scientists to measure energies as small as 1kcal/mol opening new domains of application ranging from the study of antigen-antibody interactions in the humoral immune system [1] to the characterization of the different binding modes of anticancer drugs interacting with DNA. For the latter three mechanisms of drug-DNA action have been identified: DNA elongation by unwinding (e.g. intercalation), DNA bending (e.g. by major and minor grove binding) and DNA condensation and collapse (e.g. induced by electrostatic effects and aggregate formation). The elucidation of the different mechanisms of action of anticancer drugs on essential molecules such as DNA is key to fully understand their direct and indirect effects when supplied to the patient.

In this talk I will review some of the most important results obtained in my group on this exciting field. I will start by briefly reviewing some of the results obtained in my lab in the study of *Kahalalide-F* (KF), an anticancer hydrophobic peptide that reached clinical phase trial II and contains a single positive charge that confers strong aggregative properties with DNA [2]. Our results suggest that in an *in vivo* context, the enhanced electrostatic interaction of KF due to its aggregation might mediate the binding to other polyanions such as phospholipids in the plasma membrane inducing the observed formation of pores and cell necrosis [3]. Next, I will describe results on a DNA bis-intercalator peptide *Thiocoraline* synthesized by Pharmamar (Zeltia Group) that reached clinical phase trial I. *Thiocoraline* elongates DNA by approximately 50% and shows an extremely slow off-rate (hours) that increases with force [4]. We have also determined that *Thiocoraline* binds DNA in a specific and non-specific manner via an intermediate state, with a preference for clamping CG dinucleotide motifs. Finally, single molecule methods are not only a powerful tool to dissect mechanisms of action of complex anticancer drugs, they can also be used to discriminate specific binding sites on DNA providing and efficient and accurate way to footprinting. Results for other peptide and protein binders will be shown.

References

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