Poster

Understanding the molecular basis of retinoid signaling

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Retinoic acid (RA) is one of the active metabolite forms of Vitamin A and functions as a key signalling molecule in the control of many developmental processes including differentiation, proliferation and apoptosis. Intracellular RA interacts with a range of cellular binding proteins and nuclear receptors as part of its key modulatory role in the regulation of transcription [1]. In this role, RA can be bound by Cellular Retinoic Acid Binding Proteins (CRABPs) 1 and 2. CRABP1 is solely localised within the intracellular matrix and functions as part of the non-genomic pathway, controlling a variety of RA-mediated pathways such as RA metabolism and kinase-dependent phosphorylation. CRABP2 functions as part of the genomic pathway and transports RA into the nucleus through interactions with α-importin. Within the nucleus, CRABP2 releases RA where it can be bound by two RA receptor families, Retinoic Acid Receptors (RARs) and Retinoid X Receptors (RXRs). RARs and RXRs can coordinate together through the binding of RA, along with small co-regulatory proteins, to form large heterodimeric complexes. These complexes act as transcriptional modulators to stimulate or repress the transcription of their target retinoid-responsive genes.

Retinoid signalling has been implicated in a wide range of diseases such as Alzheimer's disease, Parkinson's disease, motor neurone disease and cancer. Due to the highly diverse and powerful biological roles of retinoids in humans, studying and understanding the role of retinoids in these complex pathways is challenging as there is no singular structure-function relationship. Using a library of synthetic retinoid analogues, we are adopting an integrative approach by combining standard structural biology techniques with novel biochemical assaying methods to explore the underlying molecular basis for retinoid selectivity by both CRABPs and RAR/RXR heterodimers [2-3].

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[3] Tomlinson, C. W. E., Chisholm, D. R., Valentine, R., Whiting, A. & Pohl, E. (2018). *ACS Med. Chem. Lett.,* **9**, 1297.