

M002 The regulation of protein phosphorylation

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Protein phosphorylation is ubiquitous in almost all cellular processes reflected in the large number of protein kinases and phosphatases encoded in the human genome (518 protein kinases and 150 phosphatases). Control by phosphorylation is present in all three divisions of life but phosphorylation on serine/threonine is rare in prokaryotes and tyrosine phosphorylation is largely absent in premetazoan eukaryotes and evolved at the advent of metazoan multicellular organisms. The evolution of complex interacting pathways for regulation by phosphorylation in higher forms of life has formed a rich subject of investigation. Regulation of protein phosphorylation is frequently disrupted in the diseased state and protein kinases have become high profile targets for drug development. In this lecture I shall focus on the structural aspects of protein kinase regulation ranging from phosphorylase kinase, the first protein kinase to be identified, and its only physiological target glycogen phosphorylase to the regulation of the cell cycle through cyclins and the cyclin dependent protein kinases. Finally I shall describe one of the key regulators of transcription, CDK9/cyclin T1, which exhibits a variation on the canonical cyclin CDK interaction. Recent studies with my colleague, Sonja Baumli, have shown how CDK9/Cyclin T1 is regulated by compounds that are in clinical trials or widely used in cell biology, namely flavopiridol and 5,6-dichloro-1- β -D-ribofuranosylbenzimidazole (DRB).