Binding reactions: epigenetic switches, signal transduction, evolution and cancer

Mark Ptashne *

"Classical models tell us more than we can at first know"…Karl Popper

"Activation of transcription of a gene" – sounds fancy but, especially in eukaryotes, all we need are the simplest of reactions, binding reactions (weak ones at that) between proteins, and between proteins and DNA. Such reactions comprise bacteriophage lambda's epigenetic switch – once a gene encoding a transcriptional activator is turned on, a simple positive feedback loop maintains that expression. This logic underlies all epigenetic switches involving gene regulation that we understand, and the process lies at the heart of developmental biology.

Just as Darwin specified, lambda's switch has accrued "add-ons" that make a system that works, work better. For example, cooperative binding of proteins to DNA – effected again by weak binding reactions between them – increases specificity of binding, promotes a 'switch like' character to the system, and is used in other contexts to integrate signals. Another add on: a negative feedback loop – another binding reaction – maintains the concentration of the key regulator below a specified level, thereby helping to ensure cooperativity is not obviated.

A recasting of the mechanism of activation: the "activator" imparts 'specificity' to the RNA polymerase, i.e., determines when and where any specific gene is transcribed. This is a powerful formulation – many eukaryotic enzymes that work on other macromolecules have multiple possible substrates, and "recruiters" determine which is chosen. This picture explains how nature could evolve enzymes as disparate as humans and flies using essentially the same enzymes (i.e., change the recruiters and their binding sites). It also explains a lot of our problems – to get a quickly evolvable system to work, we need many add-ons, including (and perhaps especially) negative factors that prevent the otherwise spontaneous reactions that would occur. Cancer illustrates how easy it is for regulatory systems run by recruitment to go awry.

One way that spontaneous, low level, transcription is inhibited is by the wrapping of DNA in nucleosomes. The disposition of nucleosomes along DNA is often called the 'chromatin architecture'. As time permits I will describe recent findings that show that, and how, specific DNA binding proteins determine chromatin architecture, and what affect that architecture has on gene regulation.