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The Incarnation of CTCF

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CTCF or CCCTC binding factor is an 11-Zn-Finger (ZF) transcription factor with highly versatile functions. It is localized to the nucleus, ubiquitous, highly conserved and binds to varying target sequences to perform different regulatory role. Depending on the promoter, ZF combinations and cell type, CTCF may behave as either an activator or repressor of transcription. Two CTCF-binding sites were identified flanking the CTG repeats and form an insulator element between DMPK and SIX5 genes at Myotonic dystrophy (DM1) locus. The imprinting centre of the XIST antisense gene, Tsix, has been found to contain several tandem CTCF-binding sites. Further investigation identified that CTCF is a possible trans-acting factor in the X-inactivation pathway. We have previously identified several proteins interacting with CTCF. Two protein interacting partners of particular interest were chosen for the present project. The first protein was the Large Subunit of RNA Polymerase II (LS Pol II), the principal enzyme for transcription; and the second protein was the transcription factor YB-1, a member of the Y-box family. We demonstrated that interactions between CTCF/YB-1 and CTCF/ LS Pol II occur both in vivo and in vitro, and they are direct. CTCF employs fingers 3-6 from the Zn finger domain for interaction with the Cold Shock Domain of YB-1. Interaction with the LS Pol II occurs via at least two sites within the CTCF-C.

In this talk, I will also be discussing a CTCF paralogue, termed BORIS for Brother of the Regulator of Imprinted Sites that is firstly detected to be expressed in the testis. BORIS has the same exons encoding the 11 ZF domain as mammalian CTCF genes and interacts with similar cis DNA elements. However, BORIS encodes amino- and carboxy- termini distinct from those in CTCF. Similarity of the ZFs indicates that mammalian CTCF and BORIS proteins will recognize the same or an overlapping spectrum of DNA sequences, but the dissimilar flanking regions point out that the functional consequences of DNA binding by these two proteins are likely to be different. Expression of BORIS in normally BORIS-negative cells promotes cell growth, which can lead to transformation. As a rule, CTCF and BORIS are expressed in a mutually-exclusive pattern that correlates with re-setting of methylation marks during male germ cell differentiation. However, aberrantly expressed BORIS can take place of CTCF in vivo and deregulate CTCF targets. A rivalry caused by abnormal activation of BORIS in soma, especially in the cells where it is never normally expressed, can therefore potentially lead to cancer development.

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