**The Resurrection of the Barr Body!**

Doctors of a certain generation may have a hazy recollection of the term, "Barr body." In 1949, Dr. Murray Barr reported the identification of a dot like structure in cat nerve cells, which was seen to be always adjacent to the nucleus of the cell. This structure was exclusively seen in cells from females and never from males. It was subsequently postulated that this cytogenetic phenomenon represented an X chromosome, further evidence for this interpretation accruing in 1954 when Turner described infertile female patients with gonadal dysgenesis and short stature, in whom no Barr body was identifiable. Likewise, a Barr body was identified in tall, infertile males by Klinefelter. Since human chromosomes did not become amenable to study and direct examination until 1956, these early observations, combining clinical description with Barr body data, represented important milestones in the identification of the syndromes we now recognise as 45XO (Turner syndrome) and 47XXY (Klinefelter syndrome). Indeed, throughout the late 1950's and 1960's, study of the Barr body formed an integral part of the assessment of human infertility conditions and the identification of sex chromosome aneuploidies. By then, it had become clear that the Barr body represented a single, condensed X chromosome in female cells. Lyon's hypothesis of 1961, initially based on mouse study, but extended in 1962 to humans, was that female cells required only one functioning X chromosome and that the inactive one would appear as a condensed chromosome. This silencing of an X chromosome is achieved by the synthesis of a special type of noncoding RNA molecule, from a locus on the X chromosome, known as *Xist*. These molecules spread along the X chromosome which is to be silenced, modifying the underlying chromosome and closing the genes on that X chromosome to transcription and subsequent translation.

Little has been heard of the Barr body for several years now and, indeed, a quick straw poll among young doctor colleagues did not reveal a single individual who had heard of this medical anachronism, much less understood the significance in chromosome or gene interpretation of X inactivation. However, as is so often the case in medicine, a deeply unfashionable, indeed outdated, concept has now sprung back to prominence.

Writing in the journal, Nature, Dr. Jun Jiang and colleagues from the Department of Cell and Developmental Biology at the University of Massachusetts Medical School have shown that the *Xist* locus can be used to suppress the expression and translation of genes from a chromosome 21 in cells taken from a Down syndrome (trisomy 21) patient. In essence, these researchers used pleuripotent stem cells, still retaining their capacity to develop into any type of mature cell, from a male case of Down syndrome and inserted an inducible *Xist* containing construct into one of the 3 copies of chromosome 21. The resultant data showed that, by turning on the *Xist* gene, it was possible to dampen that copy of chromosome 21, so that the chromosome was effectively switched off. This represents a new approach to possible therapeutic intervention in Down and other chromosome syndromes, and opens the theoretical possibility of "chromosome therapy" as distinct from gene therapy. The essence of this is the functional suppression of the underlying pathology of the syndrome in living cells, which has now been shown to be possible, in vitro.

The best evidence that the repression of a single copy of chromosome 21 might have a corrective effect upon the cells and their developmental behaviour comes from the studies the authors report in respect of neural progenitor cells. Early onset Alzheimer's disease is a well established phenomenon in Down syndrome patients and neural cell differentiation in trisomic cells is markedly slower than in the cell cultures in which the chromosome 21 is suppressed. The process whereby neural development in Trisomy 21 cases is subverted to promote the emergence of Alzheimer disease is not understood but there is an assumption that the abnormal neurological differentiation is contributory. Whether these observations will have any therapeutic benefit in the future for Trisomy 21 patients is a moot point, with many scientific, ethical and legal challenges to be surmounted. Meanwhile, those with a passing knowledge of the history of cytogenetics will smile wryly at the re-emergence of the term, Barr body, which the researchers used to describe the suppressed chromosome 21 in their cell studies!

Jiang et al., Translating dosage compensation to trisomy 21. Nature 2013;550:296-300.