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The 'tether drop' hypothesis for the mechanism of chromosomal aberrations

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Chromosomal aberrations involve not only breaks in double strands of DNA, but also inappropriate rejoinings of broken ends of DNA. These abnormalities can be induced by a variety of chemical agents and also by ionizing radiations. Most theories of the mechanisms of chromosomal aberrations involve these agents directly causing double strand breaks in DNA. However, numerous observations are inconsistent with this idea. Almost no chemicals are able to break DNA strands in aqueous solutions, and the doses of radiations required to produce double strand breaks in water are much higher than are needed to produce chromosomal aberrations in living cells. Many chemicals, such as caffeine and acridines do not react covalently with DNA. Certain drugs which cause chromosomal aberrations, especially the etoposides do not react with DNA. These are known to act on enzymes (topoisomerases) which create breaks in DNA strands as part of physiological unraveling of DNA. Current theories also offer no clear explanation of in rejoinings of DNA strands.

Here it is suggested that chromosomal aberration-inducing agents act on the 'tether' component of the enzyme complexes which break DNA *in vivo* – mainly the enzymes of unraveling, synthesis, repair and transcription of DNA. During the period of time in which these complexes carry out their primary action, a component of each complex must tether the broken ends of the DNA strand in place until the last phase of the process – ligation – occurs. Thus if the tether function (often carried out by accessory proteins) of a complex were to fail while the strand-breaking site on the enzyme was acting, then broken ends of DNA could become free in the nuclear space. In relation to re-joining, if additional undamaged accessory proteins and other broken ends were also present in the same space, then the broken strands of DNA could be brought together and acted on by the ligase. All of the known forms of chromosomal aberrations, including ring forms and tri-radials, as well as deletions and amplifications, can be explained by this mechanism acting in the various phases of the cell cycle. Moreover, mutation(s) of 'tether' protein genes may contribute to the unstable aneuploidy ('karyo-unstable phenotype') in cancer cell populations.

Reference: Bignold LP (2009) Mutation Research, 681: 271-298.

Biography

Leon Bignold graduated in medicine from the University of Western Australia in 1971, completed a research doctorate 1978, qualified as a histopathologist in 1980 and has been worked in academic and diagnostic pathology ever since. He has published over 70 papers and edited vol 96 of EXS (Cancer: Cell Structures, Carcinogenesis and Genomic Instability, 2006). With colleagues, he has published a volume (2007) on David Paul Hansemann (1858-1920), who was the first to suggest a chromosomal theory of cancer. Dr Bignold is currently completing a volume on genomic models for complex clinical, pathological and therapeutic aspects of tumors.