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Sister chromatid cohesion during meiosis

Life is tough. To live, cells must not only divide to multiply but must do so correctly, again and again. The 'cell cycle' has been an area of intense recent study. Much of these studies have been done in the yeasts *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*, in vertebrate cells cultured in the laboratory and in the fruit fly *Drosophila melanogaster.* These studies bear out what is now a cliché worth repeating: The impressive evolutionary conservation of molecular players performing similar cellular functions. These studies on cell cycle and similar studies on the mechanisms of DNA and chromosome replication during the cell cycle have had immense practical relevance to medical problems. After cell division, each daughter cell must receive the correct complement of its DNA, present in the correct manner in each of its several chromosomes. To do this, the mother cell replicates each chromosome and the 'sister chromatids', the replicated chromosomes, 'stick' together to their homologs. At an appropriate time during the cell cycle, the 'sister chromatids' separate and one copy of each chromosome goes to each progeny cell.

The cell cycle can be conveniently divided into four stages. DNA replicates during the S phase and the duplicated chromosomes separate during the M phase. In the cells of our soma, as distinct from germ cells that give rise to egg or sperm, the S and M phases are separated by what are called gap or G phases. The G_1 phase occurs before DNA replication and the G_2 phase before mitosis or cell division. The progress of the cell cycle is subject to controls. There are 'internal' controls or check-points that co-ordinate cell cycle events in space and time and halt progression of the cycle in situations where irregularities occur. These check points will detect, for example, improper chromosome spindle assembly or DNA damage. Another type of control on the cell cycle are 'external controls'. The controls, which can be hormonal, controlled by growth factors or, for example, by neuronal signals; act to determine the extent and time of cell proliferation and have the effect on deciding the time of differentiation, the number of cells that will differentiate and where they will differentiate. In a multicellular organism, therefore, these controls on cell cycle are crucial in deciding the growth and form of an animal or plant. Integrating studies on cell cycle with those on the development of organisms is another exciting area of current research.

Coming back to 'sister chromatid' cohesion and separation, this aspect of the cell cycle has been studied in situations where many of the controls mentioned above fail to operate and in other kinds of situations as well: the timing of cell cycle events, the effect of cellular signaling, the dynamics of chromosome and spindle movement. Proteins involved in each of these events affect sister chromatid separation. During the cell cycle, sister chromatid separation occurs but once, after the S- and G_2 phase where cells have completed DNA replication but have not undergone mitosis. This is during the M phase. If DNA replication continues but sister chromatid separation does not occur, then cells containing many copies of each chromosome, polyploid cells, will be made. For organisms such as humans, this is not a nice thing to happen, but many plants and insects have polyploid nuclei as a normal part of their development. Alternatively, if sister chromatid separation occurs at a higher frequency than DNA replication, then cells with a reduced amount of DNA will result. This is certainly not a very nice thing to happen to a cell. Signals, responses, glues, motors, spindles: in studying the cellular orchestra that these players have organized, we are studying a very fundamental property of life – the ability to replicate and survive to replicate.

Amit Bardhan **(page 376)** addresses the mechanisms underlying the cohesion of sister chromatids during a process different from the relatively simple situations mentioned above. He focuses on meiosis, the events that take place to generate egg or sperm cells in which the chromosome number is half that of somatic cells. In this process too, sister chromatid cohesion and separation are important, critically so since the next generation is involved. Bardhan discusses evidence that suggests that different parts of the chromatids may have different mechanisms of adhesion and reviews the functions of genes that are involved in the process.

K. VijayRaghavan

Potential application of markers

Studies on the organization of genetic material, what it encodes and how it functions in the building of an organism: these are some of the areas that genome analysis addresses. Another major effect of technical advances in molecular genetic methods is the rapidity with which relatively crude maps of genomes can be generated. Given the fact that genomes of 'related'

organisms are similarly organized in many respects, even a gross map can be very useful if it can be compared with a dense map in another organism. Thus, the study of how grasses have evolved and diversified has been greatly aided by the study of the genomes of wheat and rice. Similarly, the high level of conservation of genome organization between mouse and human, although they 'separated' about 100 million years ago, allow the functional mapping of human DNA sequences that regulate the activity of genes.

Jayasankar and Dharmalingam (**page 383**) report the first steps of the analysis of the genome of two species of fish. The mapping of characteristics along a linear piece of DNA, the chromosome, requires that the characteristics be identifiable as 'similar but different'. In genome analysis these characteristics are often fragment size and sequence variation at a particular genomic location. Thus, sequence similarity identifies a location and variation in the region can be used to map this location. The polymerase chain reaction (PCR) has been applied widely as a sensitive method for genome analysis studies. Its strength lies in high level of sensitivity of the method, thereby requiring a small amount of sample. This advantage lends itself to applications such as the study of populations in the wild where sample availability is likely to be limiting. The disadvantage of the method is also its sensitivity. Many factors in the reaction can cause small variations that are amplified by the sensitive method. Reproducibility, a key to precise mapping becomes difficult. There are other methods which can overcome this problem and these use sequences called microsatellites. The identification of sequences flanking microsatellites and the use of variability in these sequences between animals is a powerful tool for mapping experiments. Jayasankar and Dharmalingam's experiments are at a very early stage, but the wide use of such methods is bound to allow the rapid genetic analysis of fish. Groups worldwide, particularly in Tubingen in Germany, have made steady progress in the study of the zebrafish, *Danio rerio*. Studies on this model organism will help in the mapping of other fish, in manner similar to what has happened in mouse and human and in plants.

K. VijayRaghavan

Caste and disease

Duchenne muscular dystrophy (DMD) is a muscle degenerative disorder afflicting almost 1 in every 3500 males. This genetic disorder is linked to the Xchromosome and is transmitted from mother to son in a recessive manner. Individuals affected by DMD do not survive beyond their late teens. In the related disease, Becker muscular dystrophy (BMD) patients struggle along until middle age, with a life span of about 40–50 years. Genetic disorders are often amplified by selective breeding amongst restricted populations. DMD occurs at a significantly higher level in Indian migrants in UK as compared to other local and ethnic groups. The disease itself is primarily a consequence of deletions in the dystrophin gene, although the precise molecular mechanisms involving the protein dystrophin remain unclear.

The identification of the gene responsible for DMD and its localization on the X-chromosome, together with polymerase chain reaction methodology, now permit analysis of the population-based variations in the incidence and pattern of gene mutations. Mishra *et al.* (**page 395**) analyse the occurrence of DMD/BMD in different caste groups in Uttar Pradesh. They demonstrate a higher prevalence of the disease in *Brahmins* and *Vaishyas*, presumably a reflection of centuries of strictly caste-based marriages. Their results, however, raise questions regarding a prevailing hypothesis that 'deletional mutations changing the translational reading frame of dystrophin should cause the severe form of the disease (DMD), but deletions still maintaining the frame, result in the milder form (BMD)'.

The ready analysis of the gene responsible for DMD/BMD offers the possibility for genetic counselling. The fact that DMD/BMD is an X-linked recessive disorder, ensures that mothers act as carriers and sons have a high chance (50%) of being afflicted. In a social mileu that places a high premium on the male child, the problems of counsellors are obvious.

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