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Editorial

Embryonal tumours and genomic imprinting

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A previous Editorial described the epigenetic process of genomic imprinting and its role in development, allowing some homologous alleles to function differently in the conceptus depending on whether they come from the mother or father. This genetically determined activity has been shown to be important in the genesis of human tumours.

In the embryonic tumours of childhood the mechanism of development of the neoplasm appears to be that two mutant alleles of a putative tumour-suppressing gene are produced, the first by mutating one allele and the second by loss of the normally functioning allele, generally as a result of genetic recombination (although meiotic non-disjunction may occur). This causes tumour tissue to become homozygous for markers located on the mutated chromosome, permitting identification of its origin. In familial cases the chromosome retained in the tumour is derived from the affected parent but in sporadic tumours the somatic mutation thought to be the cause of the neoplasm should theoretically have an equal chance of occurring in the maternal or paternal gene. This is not the case for sporadic nephroblastoma or osteosarcoma where it has been shown that the paternal chromosome is retained in the tumour while the maternal one is lost (Schroeder et al. 1987, Toguchida et al. 1989). For retinoblastoma, similar findings have been claimed but not all studies have confirmed this (Dryja et al. 1989). In the paper of Zhu et al. (1989), 9 retinoblastomas from 8 unrelated nonfamilial cases were studied using RB1 linked genetic markers. Six tumours retained the paternal allele and 3 the maternal; of the unilateral tumours only 1 retained the paternal allele. In contrast, tumours from 4 of the 5 bilaterally affected patients retained the paternal allele suggesting that, either the new germline RB1 mutations appear more readily in spermatogenesis than oogenesis or that imprinting in the early embryo affects the chromsomal susceptibility to mutation. Combining the data of Zhu and Dryja groups gives 13 of 14 bilateral tumours retaining the paternal chromosome ($0.001 < P < 0.01$) with 4 out of 10 unilateral tumours doing the same – a non-significant difference.

The tendancy for the first somatic mutation in Wilms tumour to occur on the paternal chromosome is due to genomic imprinting, presumably the Wilms locus is imprinted in embryonic kidney and the retinoblastoma locus in bone but not in retina.

Nephroblastoma results from a homozygous mutation of a gene located at chromosome 11p13 where loss of extended regions or the whole of the chromosome may occur. Several other tumours including rhabdomyosarcoma and hepatoblastoma also show loss of heterozygosity at p, suggesting that loss of the same gene can produce different tumours depending on the cell lineage in which loss occurs. In the nephroblastomas occurring as part of the Beckwith-Weidemann syndrome (BWS) deletions occur in bands 11P15.5. For retinoblastoma, similar changes occur at 13q14, a change which is also associated with a considerable increase in osteosarcomas in the survivors of the heritable form of the eye tumour. Loss of heterozygosity for 13q is also seen in sporadic cases of osteosarcoma and the retinoblastoma gene is deleted in some of these tumours.

In sporadic cases of the tumours, mutation can occur in either the paternal or maternal gametes or in the somatic cells of the embryo. The second mutation must occur in somatic cells. Toguchida et al. (1989) investigated the origin of chromosome 13 in osteosarcoma, studying a group of patients who were considered to have had somatic mutations, since none of them had had retinoblastoma. Of 13 sporadic osteosarcomas in which they found loss of heterozygosity for 13q markers, 12 retained the parental chromosome and after eliminating 3 cases about which some doubt was evident they were left with a paternal: maternal retention ratio of 9:1. In nephroblastoma the cases associated with aniridia and genitourinary anomalies and the bilateral cases are probably caused by germinal mutation, and unilateral lesions by two somatic cell events. Schroeder et al. (1987) found that in all 5 cases of nephroblastoma they studied the paternal region of 11p was retained.

The explanation of these observations is disputed (see Reik and Surani 1989). The author prefers the hypothesis

of Wilkins which suggests, on the basis of observations on nephroblastoma, that the transforming gene is imprinted. Inactivation of the nephroblastoma gene product depresses the transforming gene and results in the development of a tumour. The maternal allele of the transforming gene is rendered inactive by methylation imprinting (increased methylation of paternal DNA would allow a greater frequency of mutation by deamination of 5-methylcytosine and is known to occur in transgenic mice). Thus, the combination of the inactive nephroblastoma gene and the transforming gene of the paternal chromosome results in a tumour.

However, another plausible hypothesis exists (Sapienza et al. 1989). These authors suggest that only a small minority of cells in an embryo retain methylation differences between specific parental alleles. In these cells the maternal gene is likely to be relatively inactive because of increased methylation (an assertion based on their data from work in the transgenic mouse). If the first mutation happens on a paternal chromosome opposite the relatively inactive maternal allele, this population will expand and a focus of tumour cells will appear in the target tissue. This focus represent an increased mass of cells in which the second mutation may occur, resulting in the loss of the second allele. This hypothesis permits the attractive option that the remaining maternal allele need not be completely suppressed but may operate at a reduced level which may even vary at different stages of development. It is thus possible for the second hit not to happen, in which case "tumour-like lesions... that have regressed" may be found in the affected tissue. Whilst not much liking the authors nomenclature, it is clear that evidence of focal abnormalities of development are found in association with nephroblastoma, and the so-called neuroblastoma in-situ may represent such a focus.

The previously discussed reports of findings in the Beckwith-Wiedemann syndrome (BWS) made clear that in many patients, both copies of part of the short arm of chromosome 11 (11p15.5) come from the parental genome. Chimaeric mouse embryos containing cells partially disomic for the distal part of chromosome 7 also have features which resemble BWS and are abnormally large. The gene for insulin-like growth-factor 2 (Igf-2) lies in this region in the mouse and mouse chromosome 7 is homologous to human chromosome 11p15.5 as discussed by Little et al. (1991). In around 12–13% of BWS patients nephroblastoma, rhabdomyosarcoma or hepatoblastoma may occur, and if loss of an 11p15.5 allele occurs it is always a maternal one. The 11p15 trisomy found in a few patients with BWS always results from duplication of the paternal allele. There is tight linkage of familial BWS to 11p15.5 and the degree of homozygosity at 11p15.5 in sporadic probands is greater than that in the normal population, suggesting paternal isodisomy (two copies of the same allele from the father). The links between 11p15.5 and paternal duplication and BWS suggests that this region codes for a paternally active growth factor – or a maternally active growth suppressor. An overabundance of Igf2 messenger RNA is seen in the tumours of patients with BWS (Scott et al. 1985) suggesting abnormal activity of the gene, and abnormalities of the growth factor (or receptor) could be invoked as a mechanism for oncogenesis.

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