NEWS AND COMMENTARY

Skin Cancer

Basal cell carcinoma: genetic homogeneity in a tumour type displaying phenotypic diversity

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Last year in the journal *Cancer Research*, Teh *et al*¹ reported that 93% of basal cell carcinomas (BCCs) display loss of heterozygosity (LOH) at chromosome 9q21–q31 as the major observable genetic abnormality. These data consolidate the view that at the genomic level BCC is a relatively homogenous disease. This finding however does not explain the clinical heterogeneity regarding site of tumour presentation, histologic subtype and different clinical behaviour associated with the disease.

BCC is the most common form of cancer worldwide and while generally a low-grade malignancy, if left untreated, the tumour can locally invade causing destruction to the surrounding soft tissues.² Initial treatment usually involves surgical excision, which in the case of large tumours may require plastic surgery. Other treatments include photodynamic therapy, radiotherapy and the use of immune response modifiers (imiquimod). While rarely life threatening, the high incidence of the disease and the risk of recurrence resulting in extended clinical follow-up places a major burden on health-care agencies.

Teh *et al* have used the Affymetrix 10K single-nucleotide polymorphism (SNP) microarray to provide a high-resolution genetic fingerprint of allelic imbalance across the genome for BCC. The previous hypothesis that BCC at the DNA level is a relatively homogenous disease was a fragile one, based largely on a single study in which low density microsatellite markers were used to provide an 'allelogram' for BCC.³ However, consolidation of this view

from a more thorough examination of the genome provided by Teh *et al* adds weight to the idea that the *PTCH* gene, located within the region of LOH, is the gate-keeper tumour suppressor gene for BCC. *PTCH* is the human homologue of the *drosophila patched* gene (*ptc*), and the protein PTCH is the biological receptor for the morphogen hedgehog (HH). PTCH negatively regulates HH signalling and its inactivation leads to unscheduled activation of the pathway.

HH signalling has been extensively characterised in *drosophila* and is shown to be conserved in higher mammals where it is important in organogenesis.⁴ In the skin it is thought to regulate epithelial cell growth during hair follicle development. The present study together with numerous other reports demonstrate *PTCH* to be a classical tumour suppressor, which in accordance with Knudson's two hit hypothesis, harbours inactivating mutations, with LOH of the wild-type allele occurring in a high proportion of tumours from both sporadic and the familial form of the disease; Nevoid Basal Cell Carcinoma Syndrome.⁵ Thus, disruption to HH signalling through inactivation of *PTCH* appears rate limiting for the formation of tumour. Recently, studies using antagonists of the smoothened protein, which is activated as a consequence of *PTCH* loss, have been shown to reduce tumour formation in animal models for BCC.⁶ Such approaches demonstrate future promise for the development of a mechanism-based therapy, targeting activated HH signalling for the treatment of the disease.

BCC is classical example of a disease arising through the interaction of environment and genetics. A large body of evidence supports the view that exposure to ultraviolet (UV) irradiation in sunlight is important in influencing tumour development.² However, while significant advances have been made into understanding the molecular mechanism of tumour formation, the findings of Teh *et al* and others do not explain how perturbation of HH signalling through *PTCH* inactivation accounts for the wide phenotypic diversity associated with tumour presentation in patients with BCC. For example, there are several histological subtypes of BCC, the most frequent being nodular cystic (the type studied by Teh *et al*); superficial and morphoeic types, the latter being associated with a more aggressive phenotype. The site of tumour development can also vary. The majority of BCC appear on the sun-exposed area, although a minority of patients develop tumours on the trunk and our own studies and others have shown that these patients are subsequently at an increased risk of developing further tumours. Furthermore, age at presentation of BCC seems to be decreasing with more tumours being seen on the trunk.^{7,8}

One explanation may lay in the manner in which the HH signalling pathway is perturbed in target cells forming the tumour. This view is supported by animal models for BCC based on *PTCH* knock-outs; in *PTCH*^{-/+} mice exposed to ionising radiation, different patterns of loss of the wild-type *PTCH* allele in noninfiltrative compared with infiltrative tumours was found.⁹ The accumulating data on *PTCH* mutations in BCC show that *PTCH* can be inactivated through a variety of mechanisms including both nonsense and missense mutations. Recent work has shown that polymorphic *PTCH* alleles are associated with BCC risk in patients with sporadic disease.¹⁰ Functional studies demonstrate that mutation type can have diverse effects on *PTCH* function, ranging from complete loss to reduced activity.¹¹ In support, elegant studies in *drosophila* demonstrate that *ptc* mutant alleles can be grouped into several classes based on their effect on perturbation to HH signalling and subsequent phenotype in the fly.¹² Thus the extent to which the PTCH receptor is inactivated may affect the level

of disruption to HH signalling, thus modulating the extent of biological response, which is reflected in the malignant phenotype.

It is also clear that the genetic background in which the HH signalling pathway is perturbed will influence tumour development. Thus there will be genes that will effect susceptibility or modify the severity of the phenotype. This is highlighted in studies where *PTCH*^{-/+} mice crossed with a carcinogenesis-resistant strain developed significantly fewer BCC than those crossed with a carcinogenesis-sensitive strain.¹³ Accumulating studies demonstrate that polymorphism within genes associated with handling the results of exposure to UV, such as reactive oxygen species (GST, CYP450) or DNA repair (XPD), are significantly associated with risk of BCC development.⁸

Therefore, it is possible that the extent of disruption to HH signalling and the genetic background in which this disruption occurs may influence subsequent genetic events that lead to tumour progression in BCC. The challenge for the future lies in identifying those other loci involved in BCC development. For example, the tumour suppressor gene p53 has long been implicated in BCC development but its involvement in relation to hedgehog signalling and the phenotypic diversity observed in BCC has not been adequately studied.⁸ The advance of methodologies for studying global genomic events such as the use of SNP microarrays described by the Teh *et al* and the development of high throughput sequencing and genotyping technologies should aid in this search. Further, the establish-

ment of national blood/tumour banks such as the Biobank project (<http://www.ukbiobank.ac.uk/>) should help in the study of correlating genetic events with the diversity of patient phenotype often observed. Collectively these data might help to rationalise the use of mechanism-based therapies in this and other heterogeneous diseases ■

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Pigmentary Diversity

Identifying the genes causing human diversity

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The genetic basis of variation in skin pigmentation between people of African, Asian and European origins has only recently come under study, and is far from being fully understood. Recent work indicates that variation in a gene of the solute channel family, *SLC24A5*, may be one of the major causes of skin colour differences between European and non-European populations.¹ The conservation of linked variants around the locus in Europeans indicates