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V. Cutaneous Melanoma: Genetics and Molecular Biology

M. Pierotti

THE PURPOSE of genetic analysis of malignant melanoma is to identify genes involved in the transformation of melanocytes and melanoma tumour cell progression. Three basic approaches have been used to achieve this aim:

(a) Genetic linkage analysis on familial melanoma to identify the chromosomal location of genes which predispose individuals to melanoma.
(b) Cytogenetic analysis of tumour cells to identify frequently rearranged regions of the genome, where genes relevant to onset and/or progression of melanoma cells are located.
(c) Molecular analysis of melanomas to identify mutated oncogenes or tumour suppressor genes playing crucial roles in melanoma development.

A brief summary of the present state of the art will follow for all the three above-reported approaches.

(a) To date, the results of the studies of familial linkage analysis to identify patients who are at increased risk of developing melanoma are controversial. Bales *et al.* [1] reported that the gene for hereditary dysplastic nevus syndrome (HDNS) was on the distal part of the short arm of chromosome 1 (1p36). However, van Haeringen *et al.* [2] performed linkage studies in six large Dutch families with HDNS and did not find evidence of linkage between the putative loci for HDNS and chromosome 1p. The latter conclusion was also supported by a recent analysis of Lynch *et al.* [3].
(b) Although non-random chromosomal rearrangements of chromosomes 1, 6 and 7 have been frequently reported in melanoma, consistent changes have also been detected for chromosomes 2, 3, 4, 10 and 11, and other genetic loci have been found to be affected in this tumour (for review see [4]). Interestingly, Lynch *et al.* [5] have recently completed cytogenetic studies with two kindreds affected by familial melanoma and have found evidence of chromosome instability that is dominantly inherited. Clonal cytogenetic abnormalities were also demonstrated in the skin and naevi of affected patients. The breakage abnormalities tended to involve chromosomes 14, 3, 1, 6, 11 and 22 (in order of decreasing frequency) [5]. Correlation of these cytogenetics results with linkage data may point to possible loci or frequently involved chromosomes containing a gene (or genes) responsible for FAMMM syndrome.
(c) Oncogenes and growth factors. Early analysis by transfection of NIH/3T3 cells indicated the presence of the activated *ras* gene family in approximately 10% of the examined melanomas [6]. In addition, infection of melanocytes with retrovirus containing mutated *ras* genes resulted in a series of transformation-related changes [7], including abnormalities of chromosomes 6 (Albino A, Sozzi G, personal communication). Consequently, although it is now evident that activated *ras* genes are capable of conferring many of the characteristics of tumour progression on virus infected melanocytes, the low frequency of *ras* activation in melanoma *in vivo* suggests that alternative pathways from normal to transformed melanocytes still account for most human melanomas. In this context, a constitutive expression of the basic fibroblast growth factor (bFGF) gene has been reported in metastatic melanoma cell lines that are able to proliferate in the absence of added growth factor [8]. Although bFGF is not produced by normal melanocytes, the relevance of this finding waits to be assessed. Other oncogenes have been implicated in melanoma, mainly by their chromosomal localisation coincindent with recurrent abnormalities such as *c-myb* on chromosome 6q22 or EGF-R on chromosome 7 p12–p13. However, no firm association of these oncogenes with melanoma has ever been made. A gene which predisposes fish to melanoma and shows a high degree of homology to EGF-R has been identified in Xiphophorus [9]. This gene (Tu) represents a novel gene involved in the development of melanoma at least in that animal model.

Finally, recent indirect evidence points at *ret*, a tyrosine kinase receptor gene, as a gene potentially altered in melanoma. In fact, transgenic mice carrying the mouse metallothionein *ret* fusion gene were found to develop a

severe melanosis and melanocytic tumours [10, 11]. *Ret* is found activated by rearrangement in a consistent number of papillary thyroid carcinomas [12], and, although not fully explored in melanomas, its expression has been detected in tumours originating from the neural crest [13, 14].

(d) Tumour suppressor gene. Loss of heterozygosity (LOH) analysis of melanoma cells has indicated a high frequency of LOH at many loci on different chromosomes, again including chromosomes 1, 3, 6 and 9, but in general has also indicated a significant high chromosomal instability of these tumour cells (reviewed in [4]).

With another approach, using cell fusion techniques, Trent *et al.* [15] showed that the introduction of a normal chromosome 6 in two different human melanoma cell lines (one with a detectable 6q15 deletion) resulted in altered cell morphology and diminished cloning efficiency in soft agar, and the *in vivo* growth in nude mice correlated with the loss of the introduced chromosome 6. Unfortunately, no progress has been reported subsequently for the identification of the locus on chromosome 6 responsible for the suppression of malignant phenotype in melanoma. Finally, two recent papers have reported a very high frequency of positivity (85%) by immunostaining with p53 antibodies in two series of 83 specimens of primary and metastatic melanomas.

These findings represent one of the highest incidences of p53 mutation yet registered in a human malignancy and support the concept that alterations of this gene may be an early event in melanoma development [16, 17]. So far, a similar analysis also employing molecular techniques has not been reported.

In conclusion, although in recent years several investigations have dealt with the issue of genetics and molecular biology of melanomas, perhaps with the exception of p53, we are still far from the identification of relevant genes significantly involved in its development and progression. However, the success of the molecular approach in identifying the genes of other inherited cancer syndromes, such as retinoblastoma or adenomatous polyposis (for review see [18]), leaves us with the hope that future investigations on the molecular aspect of melanoma will provide the clue for a more successful management of this increasingly important neoplastic disease.

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VI. What Has Been Achieved by Primary and Secondary Prevention Campaigns?

R. Mackie

THE THREE main types of skin cancer are basal cell cancer, squamous cell carcinoma and malignant melanoma. In the past, basal and squamous cell carcinomas have tended to be grouped together as non-melanoma skin cancer, but there are good reasons for separating these two entities out. The exact pattern of incidence in relation to sun exposure is different between the two malignancies, and it is becoming clear that squamous cell carcinoma is a greater risk in those who are immunosuppressed.

A further problem that arises regarding basal cell and squamous cell carcinomas is incomplete cancer registration. This is because there is a continuing tendency to diagnose a proportion of these lesions clinically, and to then treat with non-excisional