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The Molecular Biology of Soft Tissue Sarcomas

Janet Shipley, Jayne Crew and Barry Gusterson

INTRODUCTION

SOFT TISSUE sarcomas are a heterogeneous group of malignant neoplasms which are generally considered to be derived from and which show features of mesenchymal tissue. The incidence of soft tissue sarcomas is in the region of 1–2 per 100 000 and they account for approximately 1% of all cancers and 2% of cancer deaths.

Although studies on soft tissue tumours have generally lagged behind those of more common malignancies such as breast and colon cancer, leukaemias and lymphomas, several key advances have been made in the last few years. Firstly, it has been well established that some inherited disorders can predispose to the development of certain soft tissue tumours, but only recently have some of the associated genes been cloned and characterised. Secondly, cytogenetic analyses have demonstrated the association of specific chromosomal changes with particular types of soft tissue tumours which may have important implications for diagnoses and, in some cases, prognoses. Lastly, gains and losses (or functional loss by mutations) of genetic material harbouring important genes are also implicated in tumorigenesis. These may be visible cytogenetically or detectable only at the molecular level.

This commentary illustrates how cytogenetic and molecular approaches can contribute towards a clearer understanding of

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the development of soft tissue sarcomas by implicating specific genes in their aetiology. The potential uses of such studies in terms of patient care will also be addressed.

INHERITABLE PREDISPOSITION TO SOFT TISSUE SARCOMAS

Several types of inherited conditions predispose to both benign and malignant soft tissue sarcomas. The development of a tumour is considered to require sequential genetic alterations [1], and it is generally believed that germline mutations contribute towards the development of cancer by reducing the number of genetic "hits" that are required compared with somatic mutation. Von Recklinghausen's neurofibromatosis (NF1) is an autosomal dominant disorder in which malignant peripheral nerve sheath tumours (MPNST) and, to a lesser extent, other sarcomas occur (reviewed in [2]). Linkage analysis showed that the NF1 locus resides on the proximal arm of chromosome 17, and the discovery of 2 patients with chromosome 17 translocations facilitated the identification of the NF1 gene located at 17q11.2. The gene product, termed neurofibromin, has a GTPase-activating protein-related domain and it is postulated that it may function in normal cells as an upstream regulator of p21*ras* which acts to suppress cell proliferation. Point mutations, deletions and insertions in the NF1 locus are accompanied by increased levels of GTP bound by *ras* supporting the role of neurofibromin as a tumour suppressor gene. It will, therefore, be of interest to examine the role of the NF1 gene in MPNST. Similar approaches have recently led to the identification of a candidate tumour suppressor gene, located at chromosome 22q12, involved with neurofibromatosis 2 (NF2) [3] which is a syndrome associated with schwannomas and meningiomas.

The neurofibromatoses are good examples to illustrate how linkage analysis can indicate the location of genes involved with the development of sarcomas associated with genetic inheritance. Clearly, linkage analysis of families affected by other soft tissue sarcomas, such as those observed in Li–Fraumeni syndrome and Beckwith–Wiedemann syndrome have and will be a valuable approach for locating and identifying genes involved with sarcoma pathogenesis [4]. Further study of the individuals in the affected families may determine the underlying gene defects with implications for early diagnosis and the possible development of new treatments.

CHROMOSOME AND DNA REARRANGEMENTS

Specific chromosome rearrangements are associated with some soft tissue sarcomas (Table 1). Of particular interest are specific chromosomal translocations that have been observed in distinct soft tissue sarcoma types. In other tumour types translocations have been found to be associated with the control of expression or rearrangements of particular genes. For example, in two types of paediatric small round cell tumours, namely Ewing's sarcoma (EWS) and primitive neuroectodermal tumours, there is an association with a reciprocal translocation t(11;22)(q24;q12). This has recently been demonstrated to involve the fusion of the human FLI 1 gene on chromosome 11 with coding sequence of the EWS gene on chromosome 22 resulting in expression of a novel protein [5]. Similarly, it has been shown more recently that particular genes and fusion products are also involved with translocations in soft tissue sarcomas. The t(2;13) translocation associated with alveolar rhabdomyosarcomas and the t(12;16) in myxoid liposarcomas are good examples of such translocations.

Table 1. Soft tissue tumour-specific chromosome rearrangements

Tumour type	Chromosome rearrangement
Alveolar rhabdomyosarcoma	t(2;13)(q37;q14)
Myxoid liposarcoma	t(12;16)(q13;p11)
Lipoma	t(3;12)(q27–28;q13–q14) t(12;various)(q13–14;various) Ring chromosomes
Leiomyoma	t(12;14)(q14–15;q23) t(1;2)(p36;p24)
Synovial sarcoma	t(X;18)(p11;p11)
Malignant fibrous histiocytoma (MFH)	t(19;?)(p13;?) Ring 19
Clear cell sarcoma	t(12;22)(q13;q12)

Alveolar rhabdomyosarcomas are aggressive tumours, predominantly of young adults, which show striated muscle differentiation and are characterised by the translocation t(2;13)(q35;q14) in approximately 50% of cases. The position of the breakpoint was localised between two markers by producing a physical map of chromosome 2 [6] and the gene involved identified as the PAX3 paired box gene [7]. The PAX genes are a highly conserved gene family that, in man, have nine members. The paired box has recently been shown to constitute a novel DNA binding motif suggesting that the PAX proteins are transcription factors. The t(2;13) rearrangement in alveolar rhabdomyosarcoma results in a chimaeric transcript consisting of the 5′ portion of PAX3, including an intact DNA binding domain, fused to a portion of a chromosome 13 gene. It remains to be determined how this novel gene fusion product is relevant to the development of rhabdomyosarcoma.

Myxoid liposarcomas are characterised cytogenetically by a reciprocal translocation between chromosomes 12 and 16, t(12;16)(q13;p11). A candidate gene called CHOP (or human GADD153) maps to the breakpoint region at 12q13 and is implicated in adipocyte differentiation [8]. This gene has recently been shown to fuse with a chromosome 16 gene [9, 10], demonstrated to have homology with the EWS gene, resulting in the production of an aberrant transcript. This may alter molecular pathways in fat cell differentiation in a way that contributes towards the development of myxoid liposarcomas. Several benign forms of soft tissue tumours, including lipomas and leiomyomas, have cytogenetically detectable abnormalities in the 12q13–15 region (Table 1). These do not demonstrate rearrangement of the CHOP gene which indicates a different breakpoint and the involvement of other genes [11]. The t(12;16) and rearrangement of the CHOP gene is thus characteristic of myxoid liposarcomas and useful diagnostically in distinguishing them from lipomas.

Cytogenetic studies have revealed that the majority of synovial sarcomas contain a characteristic chromosomal translocation t(X;18)(p11.2;q11.2) giving rise to the derivative X [der (X)] and the derivative 18 [der(18)] (Fig. 1). This translocation frequently occurs as the only cytogenetic abnormality suggesting that it is a key event in tumour development. Figure 2 illustrates the stages involved in identifying the gene(s) present at translocation breakpoints, using synovial sarcoma as an example, and how these can be applied at the clinical level. Synovial sarcoma exists as two histologically distinct types, the biphasic form which consists of both epithelial and spindle cell components, and the monophasic form which consists of only spindle cells. The less differentiated monophasic form is sometimes difficult to diagnose due to similarities with fibrosarcoma, malignant

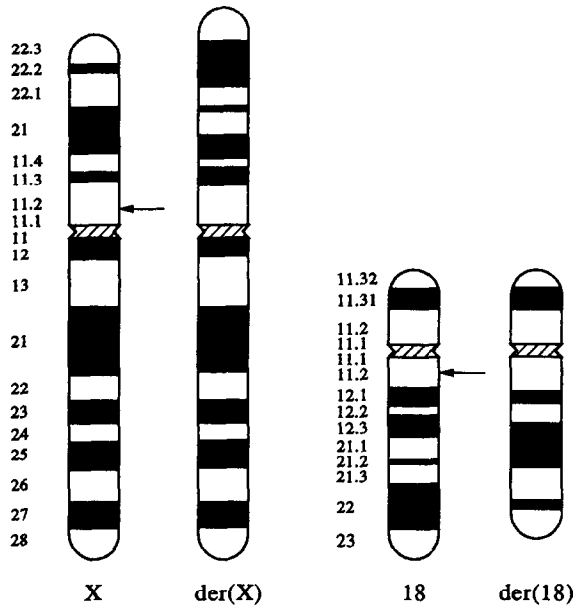

Fig. 1. Idiogram of the tumour-specific chromosomal translocation, t(X;18)(p11.2;q11.2) associated with a high proportion of synovial sarcomas. The arrows indicate the breakpoint regions.

fibrous histiocytoma and malignant schwannoma. The t(X;18) translocation is present in both forms and is, therefore, a useful diagnostic marker. Molecular approaches outlined in Fig. 2 are being used to identify genes present at the translocation breakpoint which may be involved in the development of synovial sarcoma [12–15]. Two discrete breakpoint regions on the X chromosome have been identified, both of which are in the region of sequences that are homologous to the ornithine aminotransferase (OAT) gene [13, 14]. It will be intriguing to determine whether this apparent heterogeneity of translocation breakpoints is consistent with a unifying molecular biological pathway in these tumours.

The observation that specific chromosomal translocations are present in discrete types of soft tissue tumours may revolutionise the diagnostic approaches used in these tumours. The use of cytogenetics combined with classical histological methods should provide a more reliable method of diagnosis. In addition, cytogenetic analysis has been demonstrated to assist in the prognosis of malignant fibrous histiocytomas where rearrangement of chromosome 19 is indicative of local recurrence [16]. Further cytogenetic studies of soft tissue sarcomas may reveal other such examples. Following molecular studies such as those described for specific translocations it may be possible to design polymerase chain reaction (PCR) primers that can be used to specifically amplify and detect the presence of chromosomal translocations. However, this is limited by the variations in the DNA sequence at which the breaks occur and by the maximum size of DNA which can be amplified. Alternatively, if a novel fusion protein is produced, aberrant transcripts may be detected by reverse transcriptase PCR. These approaches may provide a more rapid and sensitive method of diagnosis compared with cytogenetics. Consequently, they may also be of use in determining the efficacy of treatments by providing a method of looking for metastases and residual disease. Characterisation of fusion proteins produced as a result of a translocation may provide specific targets for antibodies useful in diagnosis or immunotherapy. Tumour-specific proteins may also provide targets for antisense oligonucleotide therapy.

GAINS AND LOSSES OF GENE FUNCTION

Molecular analysis of many tumours has revealed loss of heterozygosity of a particular locus. This is indicative of a deletion in one homologue or loss and subsequent duplication of one mutated homologue resulting in homozygosity for that locus. This suggests that the function of a tumour suppressor gene has been lost, by deletion and mutation. Molecular analysis of this type in embryonal rhabdomyosarcoma, a tumour of striated muscle predominantly found in children, has implicated the loss of a tumour suppressor gene at the 11p15.5 locus as being crucial to its aetiology [17]. The actual gene has yet to be identified.

Homozygous deletions, rearrangements and point mutations in p53 are among the most common lesions observed in human neoplasms [18]. These structural alterations which result in p53 inactivation have been observed in several sarcoma types indicating they may have a role in their tumorigenesis. Recent studies suggest that wild type p53 may have a function as a transcription factor in the control of cell differentiation and/or apoptosis. In addition, following DNA damage p53 levels have been observed to increase resulting in the arrest of cells in the G1 phase of the cell cycle [19]. Structural alteration of p53 may mean that these functions are lost. Recently, it has also been shown that wild type p53 may be bound and inactivated by the protein MDM2. The gene encoding for MDM2 has been mapped to 12q13, a region which has been observed to be amplified in a proportion of liposarcomas and malignant fibrous histiocytomas (MFH). Amplification has been shown to be associated with an overabundance of the MDM2 protein and is, therefore, an alternative pathway to structural alterations which results in the functional loss of wild type p53 [20]. Determining the biochemical function of aberrant gene products may make it possible to design more effective drug therapies. If the loss of growth control has been induced by the overproduction of a protein, it may be possible to block that specific stage of the biochemical pathway. Alternatively, if a rearrangement results in the loss of function of a gene, replacement therapy may become possible through advances in delivery systems.

PROSPECTS

There is no doubt that progress has been made towards understanding the molecular biology of some soft tissue sarcomas. Linkage analysis of families with inherited disorders that predispose to tumour development has been shown to be a valuable approach in locating regions where genes potentially relevant to soft tissue sarcoma development reside. This approach should continue to be important.

The observation that specific chromosome rearrangements are present in certain tumour types has been used routinely for years in diagnosis and as prognostic indicators in haematological malignancies. As unique chromosome rearrangements have been identified in soft tissue sarcomas, there is scope for similar potential benefits in applying cytogenetic and molecular techniques to these tumours. Particular genes have already been shown to be involved with the translocation t(2;13) in alveolar rhabdomyosarcoma and the t(12;16) translocation in myxoid liposarcoma. It may also be possible to identify other consistent primary rearrangements in specific soft tissue sarcomas which

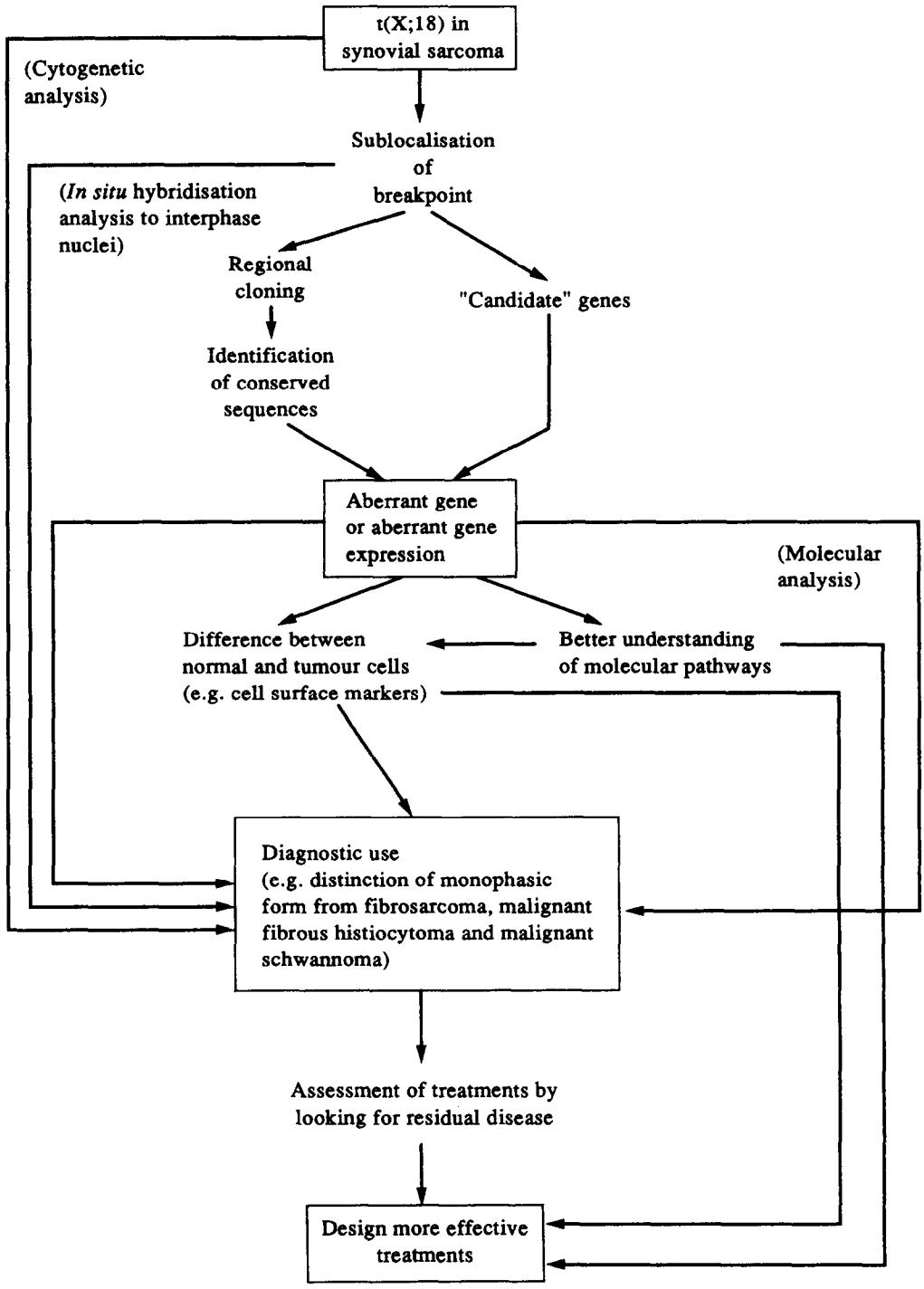

Fig. 2. Possible approaches to studying and the potential benefits of analysing a tumour-specific translocation such as the t(X;18) in synovial sarcoma.

will lead the way to identification of aberrant genes, such as in synovial sarcoma, with the potential benefits for diagnosis that have been discussed. Similar advantages are to be gained from the identification of genes normally acting in some way as a tumour suppressor and the function of which is lost in specific soft tissue tumour types. Ultimately, a molecular approach such as reverse transcriptase PCR may provide the definitive diagnosis. Finally, the challenge remains to elucidate the details of the important molecular pathways in cells and to determine how they are disrupted in tumour cells. This should reap rewards in terms of understanding the development of soft tissue sarcomas, identifying diagnostic and prognostic indicators, and potentially help in designing specific and more effective treatments.

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Environmental Tobacco Smoke and the Risk of Cancer in Adults

Jean Trédaniel, Paolo Boffetta, Rodolfo Saracci and Albert Hirsch

The apparent effect of environmental tobacco smoke (ETS) exposure on cancer risk has become an important social and political issue. The risk of cancer in non-smokers is often the main reason for prohibiting or restricting smoking in public places. A number of epidemiological studies have shown an association between ETS exposure and lung cancer. However, the strength of this association has still to be estimated. Only a few studies have reported on ETS and cancer from sites other than the lung in adults. No definite conclusions can be drawn at present from a critical review of the epidemiological evidence, but the suggestion of an association is present for sinonasal cancer, while bladder cancer does not seem to be associated to ETS exposure. Positive studies are available for cancers from other sites, including the breast, the uterine cervix and the brain, but these are difficult to interpret.
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INTRODUCTION

CIGARETTE SMOKING has been identified as the single most important source of preventable morbidity and premature mortality [1–6]. The production of lung cancer is by far the most important carcinogenic effect quantitatively, as lung cancer is now the most common fatal cancer throughout the world [7], and is expected to increase further in the future [8]. Moreover, further evidence has linked tobacco smoking with cancers of the larynx, oral cavity, oesophagus, pancreas, bladder, kidney, stomach and the uterine cervix [9].

Passive smoking, involuntary smoking and exposure to environmental tobacco smoke (ETS) are used synonymously to describe the involuntary exposure of non-smokers to tobacco combustion products generated by smokers. ETS comprises the amount of tobacco smoke which is not inhaled by the smoker (sidestream smoke), as well as the portion of inhaled smoke

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