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Special Paper

The Marriage of Pathology and Genetics in Soft Tissue Tumours: EACR—Mühlbock Memorial Lecture

H. Van den Berghe

Centre for Human Genetics and Flanders Institute of Biotechnology, University of Leuven, B-3000 Leuven, Belgium

INTRODUCTION

THEORIES ON the origin of cancer have been formulated in the past, but it is modern genetics that has brought forward more definite answers to questions about the basic mechanisms of controlled and uncontrolled cell proliferation.

The development of cancer genetics, apart from earlier observations on the familial occurrence of some cancers, started in 1960 with the discovery of the Philadelphia chromosome [1]. This acquired structural chromosome change was a somewhat lonely precursor, followed by the description of other such characteristic chromosome abnormalities after chromosome banding techniques had been developed. As a result, a wealth of specific chromosome changes has been discovered. Most human leukaemias and lymphomas have by now been well characterised cytogenetically, although some more rarely occurring entities are still being identified. This newly acquired genetic information has been integrated into routine diagnostic procedures, and disease classification adapted accordingly after correlation and combination with morphology, histochemistry and immunology [2]. The chromosome changes have not only contributed to better diagnosis, but also proved to be informative and predictive with regard to sensitivity to therapy, prognosis and survival. Progressive deciphering of the molecular lesions underlying the chromosome changes showed that the latter were instrumental in converting normal proto-oncogenes into uncontrolled oncogenes, pointed to new therapeutic strategies, such as the use of retinoic acid in t(15;17) acute promyelocytic leukaemia, and announced more remote perspectives of genetic therapy. As it is impossible to provide, in a correct way, references for the whole of the very condensed information, the reader is referred to a few sources which contain more detailed overviews on chromosomes in human cancer [3, 4], chromosomes in soft tissue tumours [5–7], molecular aspects [8–12] and pathology of soft tissue tumours [13].

Correspondence to H. Van den Berghe.
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As in leukaemia, cytogenetic investigations in solid tumours discovered a very early precursor: the 22q deletion in meninglioma, later also found in bilateral vestibular schwannoma, now part of a group of tumours known as Neurofibromatosis type 2 (NF2) and already partly characterised molecularly [15]. Among the early detected chromosome changes were also those in retinoblastoma (deletion 13q) and nephroblastoma or Wilms' tumour (deletion 11p). Both were preceded by the discovery of constitutional chromosome changes in malformative syndromes and, combined with Knudson's hypothesis on the two or more step mechanism in the genesis of cancer, would lead to the concept of suppressor genes, necessary to the control of cell proliferation. Their still largely unknown normal functions can be lost by deletion, mutation, alternative splicing, mutation of a promotor gene or methylation. One dysfunctional allele may be inherited from a parent and this is the basis for virtually all so-called major predisposition cancer family syndromes which clinically are dominant, but which are recessive at the level of the cell. The list of these disorders is probably almost complete and contains only one oncogene: *RET* [16]. Mutations in the normal *RET* gene, which codes for a tyrosine kinase receptor, transforms it into an ocogene with the mutant allele dominating over the normal one. This observation shows that hereditary transmission of an oncogene in man is not necessarily lethal.

In sporadic solid tumours, and particularly in the prevalent epithelial tumours, such as breast, colon, lung and prostate, suppressor gene alteration apparently plays a preponderant role. In sarcomas, however, activation of genes acting as oncogenes is clearly more frequent. Much of this new information has been gathered following the discovery of tumour-specific chromosome changes. The identification of specific chromosome changes in solid tumours has occurred years after that in haematological malignancies for a number of reasons, mostly related to obtaining and examining representative tumour cells. The number of viable cells obtained in culture is often rather low, as is their mitotic activity. Hence, the danger that even after one passage *in vitro* normal fibroblasts overgrow the tumour cells is a real one. Adding collagenase to the tumour sample when prepar-

ing a tumour cell suspension proved to be simple, important technical improvement, and after 1985, a series of characteristic chromosome changes quickly emerged. Comparison with those obtained in haematological malignancies showed great similarities, but also important differences. As in haematological malignancies, the vast majority of solid tumour show consistent clonal chromosome changes, whereas within each disease type a varying proportion may show a normal karyotype. In as much as they are already known, the underlying molecular lesions are also not of a totally different nature. An important difference between the two systems is that in haematological disorders the presence of an acquired chromosomally distinct clonal change invariably indicates a clinically malignant disorder. In contrast, in solid tumours, clonal chromosome changes may characterise totally innocent benign tumours such as lipomas. Unlike leukaemias, but very much like most lymphomas, karyotypic changes in solid tumours may often be extremely complex, especially in the more common epithelial tumours such as lung, breast, prostate or colon, in which no unique diagnostically useful chromosome changes have been demonstrated. In therapy-related or environmentally induced so-called secondary leukaemias, several specific chromosome changes within the same cell are often seen, and each individually may characterise a secondary leukaemia. In solid tumours, this phenomenon is much less frequently observed, although lipoma cells have been seen with simultaneous involvement of 12q and 6p, and leiomyomas with t(12;14) and 7q-, two common characteristic changes. Finally, characteristic chromosome changes in solid tumours are different from those in leukaemia and lymphoma. At the molecular level, both groups of malignancies tend to involve different genes, with some exceptions: *RAS*, activated in a whole series of malignancies, *P53*, altered or lost in around 50% of all cancers and *FUS(TLS)*, located in 16p11, involved in fusion with *CHOP* in the classical Myxoid Liposarcoma as well as in fusion with *ERG* in a subtype of acute myelogenous leukaemia [17]. The *ERG* gene in turn is involved in fusion with the *EWS* gene on 22q12 in a cytogenic variant of Ewing's sarcoma. It would not be surprising, therefore, to see in the future more of such genes being shared by haematological malignancies and by solid tumours, although a large overlap does not seem to exist.

As in leukaemias, genetic analysis can be used in the diagnostic procedures of solid tumours and geneticists and pathologists should be partners in this modern nosological approach, as will be illustrated for soft tissue tumours.

GENETICS AND PATHOLOGY IN SOFT TISSUE TUMOURS

Mesenchymal or soft tissue tumours constitute a very heterogeneous group of tumours, more than 200 in number, and comprise benign, borderline or locally aggressive, and malignant metastasising types. They represent various histotypes, all derived from a primitive undifferentiated mesenchymal cell of the mesoderm. Histogenesis is known in many, but there are sarcomas whose histogenesis is debated or unknown. There morphological appearance is kaleidoscopic and extremely wide. Hence, classification is often difficult and the subject of continuous debate among pathologists who, always with good reason, often dispute where to put a tumour in this, their battlefield par excellence.

Pathologists use ancillary methods to support light microscopy, and a diagnosis most often can be reached with the aid of immunochemistry using a steadily increasing panel of antibodies and antigen retrieval. There are, however, limitations, for example the lack of absolute tissue-specific or tumour-specific antibodies, absence of a distinct diagnostic immunophenotype, occurrence of aberrant and unexpected immunostaining and deficiency in the amount of antigen. Leiomyosarcoma can express keratin, rhabdomyosarcoma can immunostain for neuron specific enolase (NSE) and high-grade malignant sarcomas sometimes only express vimentin, a common cytoplasmic filament in musculoskeletal tumours. Immunochemistry applied on fine needle aspiration (FNA) can be difficult since soft tissue tumours often require a panel of several antibodies and the amount of aspirated material may be restricted.

DNA ploidy has been used previously in the diagnosis of leukaemia and is also being used in solid tumours to gather information on the malignant character of the tumour, the assumption being that aneuploidy would be a hallmark of malignancy. Some benign tumours, however, turn out to be aneuploid, whereas many malignant tumours are diploid or pseudodiploid. This technique is very unreliable and has no future for diagnostic purposes.

Transmission electron microscopy may contribute to diagnosis by the recognition of diagnostic structures at high resolution. Specific features to be looked for in the cytoplasm are size and pattern of filaments, glycogen, microtubules, neurosecretory granules, crystalline structures or, for example, melanosomes in various stages in clear cell sarcoma. To allow this, satisfactory preservation of the tissue is an absolute prerequisite and, ideally, small samples obtained, such as FNA, should be fixed immediately.

Electron microscopy is particularly helpful in the diagnosis of spindle cell tumours, small cell malignancies, sarcomas where other techniques are inconclusive, and sarcomas with unusual clinical presentations. Limitations occur when a tumour is poorly differentiated, not showing any single ultrastructural feature by which the origin of the neoplastic cell can be recognised, for example high-grade malignant sarcomas such as pleomorphic leiomyosarcoma and malignant peripheral nerve sheath tumour. Limitations also occur when the material is not sufficient, as in rhabdomyosarcomas with sparse filaments in only a few cells, necessitating the investigation of large numbers of cells, and in fibrocytic tumours from which it is sometimes hard to obtain enough material by FNA [18].

Genetic investigations as an auxillary method also have a series of limitations: without suitable metaphases, no chromosome analysis or *in situ* hybridisation on chromosomes is possible. Alternatively, chromosome analysis, molecular cytogenetics and molecular assays may become increasingly useful in the diagnostic approach of solid tumours in general, and of soft tissue tumours in particular.

GENOMIC CHANGES AND THE HISTOLOGICAL CLASSIFICATION OF SOFT TISSUE TUMOURS

Soft tissue tumours are a category of tumours on whose histological classification an unanimous agreement among pathologists is difficult to obtain. For the purpose of this paper, the WHO classification which classifies more than 200 entities in several groups will be followed [19].

Table 1. Specific (primary) chromosome changes in soft tissue benign tumours

Benign	
Lipoma (ordinary)	t with 12q15/t with 6p21-22/13q-
Lipoblastoma	t with 8q11-13
Hibernoma	t with 11q13
Spindle cell and pleomorphic lipoma	loss of 16q13-qter
Leiomyoma (uterus)	t with 12q14-15/7q-/ + 12/13q-/t(1;2)(p36;p24)/t with 6p21-22/3q-
Tenosynovial giant cell tumour	t with 1p11/t with 16q24
Schwannoma	-22
Myxoma (cardiac)	t with 12p12
Palmar fibromatosis	+ 7/ + 8
Biphasic tumours	
Endometrial polyp	t with 6p21-22/t with 12q14-15
Pulmonary chondroid hamartoma	t with 6p21-22/t with 12q14-15

Indications will be given in this overview on where reliable information on genomic changes is already available for each of the groups (Tables 1–4). This overview will be concluded with the adipose tissue tumours, for which a collaborative study has been set up between multidisciplinary teams from the Universities of Lund and Leuven, and preliminary results of this study will be presented.

Fibrous tissue tumours

Clinically, three subcategories can be distinguished here: benign tumours, fibromatoses and true malignancies. In the benign tumours, few cases have been investigated cytogenetically, and normal karyotypes or inconsistent changes have been observed. In the fibromatoses, however, the superficial palmar-plantar Dupuytren contracture exhibits trisomy 8 which is also found in the deep-seated desmoid tumours. In these desmoid tumours, clones may be found with trisomy 8, others with trisomy 20, and in some other cells both trisomies are present together [20]. Desmoid tumours occurring in the context of Gardner's syndrome have been shown to present 5q rearrangements which may perhaps be more related to the polyposis than to the desmoid tumour as such. Among the malignant fibrous tissue tumours, the adult fibrosarcoma as a separate entity has almost disappeared from the literature. The congenital or infantile fibrosarcoma has numerical changes only, with trisomy 11 as the more frequently occurring trisomy [21]. This tumour is locally aggressive, will usually require amputation, but is not metastasising and does not require heavy auxilliary treatment. Although not absolutely pathogenomic, the chromosome changes in this type of tumour may help in the choice of the adequate treatment.

Fibrohistiocytic tumours

No consistent karyotypic changes have yet been reported in the benign tumours belonging to this group. In the pathologically very complex malignant group of fibrous histiocytomas (MFH) karyotypes are mostly abnormal and complex, with perhaps involvement of the 19p13 region.

In the group of intermediate malignancy, two tumours are progressively becoming characterised genetically. The dermatofibrosarcoma protuberans cytogenetically shows extra ring (80%) or extra marker chromosome(s) (20%) in which material from chromosome 17 and of 22 is involved [22]. The giant cell fibroblastoma has been shown to present a t(17;22) and sometimes some extra material derived from the two involved chromosomes. It may very well be that both tumours share a t(17;22) or a somewhat more complex rearrangement of both chromosomes. Both are CD34 positive and may be one and the same tumour or very closely related forms [23]. Results from molecular studies are not available.

Smooth muscle tumours

Two entities need to be discussed here, both organ-specific: the most frequent of all tumours in man, the leiomyoma of the uterus and the intestinal leiomyosarcoma. Uterine leiomyomas which can be found anywhere in the uterine tissues and are often multiple, cytogenetically present seven different types. Half of all leiomyomas are chromosomally normal. The other half has one of six possible consistent chromosome changes. The most common among these involve the 12q13-15 region in a translocation with chromosome 14 as a preferential partner. Equal in frequency is a deletion of 7q, followed by anomalies involving 6p. Much more rare are a trisomy 12, a translocation t(1;2)

Table 2. Specific (primary) chromosome changes in soft tissue borderline/locally aggressive neoplasms

Atypical lipomatous tumour* (Atypical lipoma/well-differentiated liposarcoma)	+ ring or long marker (sequences 12q13-q15)
Dermatofibrosarcoma protuberans*	+ r(sequences 17q and 22q)
Congenital fibrosarcoma*	Combination of trisomies (8, 11, 17, 20)
Giant cell fibroblastoma	t(17;22)(q21;q13)
Aggressive angiomyxoma	t with 12q14-15
Desmoid tumours	+ 8/ + 20/ + 8, +20

* Occasionally metastasis—usually if they undergo high-grade transformation.

Table 3. Specific (primary) chromosome changes in soft tissue malignant tumours

Liposarcoma (myxoid/round cell)	t(12;16)(q13;p11) t(12;22)(q13;q12)
Leiomyosarcoma (GI)	Monosomy 1p12-1pter with hypodiploid chromosome number
Rhabdomyosarcoma (alveolar)	t(2;13)(q35;q14)/t(1;13)(p36;q14)
Synovial sarcoma	t(X;18)(p11.2;q11.2)
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22-q31;q12)
Ewing's sarcoma (PNET)	t(11;22)(q24;q12)/t(21;22)(q22;q12)t(7;22)(p22;q12)
Clear cell sarcoma	t(12;22)(q13;q12)
Desmoplastic small round cell	t(11;22)(p13;q12)
Alveolar soft part sarcoma	t with 17q25
Mesothelioma	1p-/3p-/6q-/9p-/t with 12p13
Endometrial stromal sarcoma	t(7;17)(p15:-21;q12-21)

and deletions of 3q [24]. Molecularly, some information is already available for the 12q region where the *HMGIC* is involved [25]. There is no information as yet about the molecular changes in the 14 translocation partner or in the other structural abnormalities. With regard to the malignant tumours in this group, the leiomyosarcoma of the gastrointestinal tract is the only site where chromosome changes have been found. They include hypodiploidy with consistent loss of 22, and a structural change: a deletion of 1p11-12.

Striated muscle tumours

One type of striated muscle tumour, the alveolar rhabdomyosarcoma, is well characterised both cytogenetically and molecularly. Two variant translocations occur involving chromosome 13 and either chromosome 1 or 2. Molecularly, the gene involved on 13 is *FKHR*, a putative transcription factor. The genes involved on 1 and 2 are from the *PAX* family: *PAX7* on 1 and *PAX3* on 2. The result of the translocations is a novel fusion gene and a chimeric gene product [10].

The other rhabdomyosarcomas constitute a problem to the pathologist as well as to the geneticist. Some cases, coined as solid alveolar rhabdomyosarcoma or embryonal rhabdomyosarcoma, seen to present the same t(2;13), as in the alveolar type [26]. In embryonal rhabdomyosarcoma, no consistent structural abnormalities have been documented so far.

Endothelial tumours and perivascular synovial tissue tumours

No consistently occurring chromosome changes have been reported.

Table 4. Molecular genetics in soft tissue tumours

Translocation	Disease	Affected gene
t(11;22)(q24;q12)	Ewing's sarcoma/PNET	*FLI1* (11q24) *EWS* (22q12)
t(21;22)(q22;q12)	Ewing's sarcoma/PNET	*ERG* (21q22) *EWS* (22q12)
t(7;22)(p22;q12)	Ewing's sarcoma/PNET	*ETV1* (7p22) *EWS* (22q12)
t(12;22)(q13;q12)	Clear cell sarcoma	*ATF1* (12q13) *EWS* (22q12)
t(12;16)(q13;p11)	Liposarcoma (myxoid/round cell)	*CHOP* (12q13) *FUS* (16p11)
t(12;22)(q13;q12)	Liposarcoma (myxoid/round cell)	*CHOP* (12q13) *EWS* (22q12)
t(2;13)(q35;q14)	Rhabdomyosarcoma (alveolar)	*PAX3* (2q35) *FKHR* (13q14)
t(1;13)(p36;q14)	Rhabdomyosarcoma (alveolar)	*PAX7* (1p36) *FKHR* (13q14)
t(X;18)(p11.2;q11.2)	Synovial sarcoma	*SYT* (18q11.2) *SSX1* (Xp11.2) *SSX2* (Xp11.2)
t(11;22)(p13;q12)	Desmoplastic small round cell tumour	*WT1* (11p13) *EWS* (22q12)
t(9;22)(q22-q31;q12)	Chondrosarcoma (extraskeletal myxoid)	*TEC* (9q31) *EWS* (22q12)
t(12;V)(q15;V)	Lipoma (ordinary)	*HMGI-C* (12q15) *LPP* (3q27)

Synovial tissue tumours

Some preliminary information is available on the benign tenosynovial giant cell tumours with their characteristic morphology. These tumours may occur in a localised or in a more diffuse type. In the localised form, two different karyotypic changes seem to occur. One involves 1p11 in a translocation with chromosome 2 or with another chromosome. A second type involves 16q24 without obvious preference for a partner chromosome [27]. The diffuse type so far only shows simple but different numerical changes.

The so-called malignant synovial sarcoma is discussed here, but awaits a more definite classification. It is characterised cytogenetically as well as molecularly. Translocation occurs between chromosome 18 and presumably two adjacent loci on the X-chromosome. One of these translocations may be more associated with the monophasic type, the other with the biphasic type. These presumably distinct entities have also partly been elucidated molecularly. The gene involved on chromosome 18 is *SYT* which is unrelated to any known gene, but contains a predicted glutamine-proline-glycine-rich region, suggestive of a transcriptional activation domain. The genes involved on the X-chromosome are called *SSX1* and *SSX2* and are also unrelated to other known genes. The translocation leads to the formation of a chimeric transcript as in other sarcoma translocations.

Mesothelial tumours

Again this is a type of tumour which does not belong to soft tissue tumours and must await a better classification. Malignant mesotheliomas cytogenetically are very complex and apparently heterogeneous. There is, however, a pseudodiploid subgroup which is being delineated, involving the short arm of chromosome 12 in p13. We have constructed a physical map of a 4–6 centimorgan region that contains the breakpoint in 12p13 [28] and are at present attempting to identify the molecular lesions.

Neural tumours

In the WHO classification, a whole series of tumours is classified into this group, but data on genomic changes are available only on one benign and three malignant varieties.

The benign so-called schwannoma or neurilemoma is characterised by monosomy 22. The tumour must be related to or be part of the NF2 neurofibromatosis group. To the NF1 or NF2 also must belong the malignant peripheral nerve sheat tumour, previously called malignant schwannoma. Karyotypes are very complex but chromosomes 17q and 22q are always involved [29]. The malignant clear cell sarcoma, sometimes called melanoma of the soft parts, is a rare and aggressive tumour of tendons and aponeuroses. It is now characterised cytogenetically and molecularly. The characteristic chromosome change is a t(12;22)(q13;q12). The molecular lesion consists of a fusion between the *EWS* gene on 22 and a transcription factor *ATF1* on 12q with oncogenic conversion of *EWS* and production of a hybrid molecule [10].

A third malignancy in this group, the neuroblastoma, has been investigated intensively but has not revealed its molecular secrets. Tumour metaphases characteristically show amplification of *N-MYC* localised in 2p, manifesting itself as double minutes or as a homogeneously staining region (HSR) and a variable deletion of 1p in a diploid or near-triploid karyotype. The deletion of 1p can be visualised on interphase nuclei, which may be helpful in a quick diagnostic approach. Prognostically, it is the presence or absence of *N-MYC* amplification more than the type of chromosome changes which seems to be important.

Peripheral neuroectodermal tumours (PNETs) are a group of malignancies previously called Ewing's sarcoma (extra skeletal or osseous) including also peripheral neuroepithelioma, Askin's tumour and esthesioneuroblastoma, which is a rare tumour of the olfactory epithelium. The central karyotypic anomaly is a t(11;22) with two variants found in Ewing's sarcoma: a t(21;22) and a t(7;22), and a der(16)t(1;16) as a secondary change. Molecularly, the result of the t(11;22) is a fusion of the *EWS* gene with a truncated transcription factor *FLI1* on 11q24 belonging to the *ETS* family, resulting in an oncogenic conversion of the *EWS* gene, the normal function of which is still unknown. The gene contains an RNA-binding domain in the C-terminal portion and a region with transcriptional activating property in its N-terminal half, and is ubiquitously expressed. The other translocations occurring in less than 10% of cases also result in fusion between *EWS* and a member of the *ETS* family, *ERG* on 21 and *ETV1* on 7p22 [30].

For pathologists, these characteristic changes are very welcome as they permit correct diagnosis of those members of the difficult small, blue, round cell tumours in which histochemistry is of little help [31] and to which belong neuroblastomas, alveolar rhabdomyosarcomas, intra-abdominal desmoplastic small round cell tumours, and some lymphomas, in addition to PNET. In all these cases, chromosome analysis will provide a quick and accurate diagnosis.

Paraganglionic tumours and pluripotent mesenchymal tumours

No data available at present.

Cartilage and bone tumours

A number of tumours in this group has not yet been investigated. There are preliminary observations in soft parts chondroma indicating that chromosomes 6, 11 and 12q are involved.

Among the malignant tumours, one anomaly stands out: the t(9;22)(q22;q12) in extraskeletal myxoid chondrosarcoma. This characteristic chromosome change is not found in other types of chondrosarcoma. Molecularly, the *EWS* gene on 22q this time fuses with *TEC*, the promotor region of *EWS* causing oncogenic conversion of *TEC* which is an orphan nuclear receptor [32].

Miscellaneous and unclassified soft tissue tumours

Among the benign tumours listed here, the cardiac myxoma, which may show a rearrangement of 12p12 [33], and the angiomyxoma, with involvement of the *MAR* region 12q13-q15, must be mentioned [34]. Of the malignant tumours, several entities have been characterised. The alveolar soft part sarcoma shows involvement of 17q25. The extra-renal rhabdoid tumour, when located in the brain,

shows monosomy 22 and should be further investigated for its relationship with NF2. When located elsewhere this tumour has so far failed to present consistent chromosome changes, and the rather minimal karyotype anomalies seemingly contrast with the highly malignant behaviour of this tumour. The intra-abdominal desmoplastic round cell tumour is also a highly malignant disease and can be grouped with other small, blue, round cell tumours in which histochemistry is of little help to the poor resolution of morphology. This tumour is characterised by a t(11;22)(p13;q12) and molecularly results in oncogenic activation of the *EWS* gene by the Wilms' tumour gene (*WT*), a unique example of a suppressor gene causing oncogenic conversion of another gene [35]. The *EWS* gene, in its involvement in cancer, thus shows some promiscuity since it is involved in six different disorders [36].

Looking back upon all these anomalies, there are, in the sarcomas, striking similarities among the translocations with the possible exception of the t(X;18) about which we know so little. All result in the production of a tumour-specific chimeric RNA transcript which is predicted to encode a novel oncogenic transcription factor, very much as in leukaemias. Furthermore, several of the translocations result in the rearrangement and fusion of a gene having an RNA binding domain such as *EWS* and *FUS* with a transcription factor (*FLI, ERG, ETV, ATF1, CHOP, WT*).

Looking at the partner genes in the translocations, a model seems to be emerging in which the translocation partner supplies the DNA binding domain conferring the target specificity of the transcriptional activation mediated by the chimeric protein, the different translocation partners of *EWS* apparently being responsible for the biological differences. This situation may be similar to that of the *MLL* gene in 11q23 in leukaemia, and perhaps also to that of the *HMGIC* gene in benign tumours.

Genomic changes and morphology in adipose tissue tumours: the CHAMP experience

The tumour types in which integration of genetics and pathology has been most fruitful are the adipose tissue tumours. To promote this integration, a study group was set up between the Universities of Lund and Leuven, and their respective specialists in the relevant disciplines. The group which also has some U.S. based experts in pathology of soft tissue tumours is called CHAMP [37]. The main results of this collaborative effort are as follows.

Benign tumours. Cytogenetically, lipoma, in half the cases, shows a normal karyotype. In the other 50%, three subgroups can be identified: (1) a major group involving 12q13-15, with several possible partners, of which 3q27 is a preferential one; (2) a deletion of 13q; (3) a rearrangement of 6p21-22. Molecularly, the target gene in 12q15 is a member of the high mobility group protein gene family, *HMGIC*, which, in its preferential translocation with #3, fuses its DNA binding modules to the protein-binding interfaces of the protein of a gene called *LPP*, which shows sequence similarity to the LIM protein family. The members of this family all possess so-called LIM domains, i.e. cysteine rich, zinc-binding protein sequences found in transcription regulators, proto-oncogene products and adhesion plaque constituents, and are postulated to have a role in cell signalling and control of cell fate during development.

Hibernoma is a rare tumour, with characteristic pathology showing fine vacuolated brown fat cells. Cytogenetically the 11q13 region is involved in all cases examined.

Lipoblastoma also is a rare tumour, by definition occurring in children. Age of the patient and the finding of a specific 8q rearrangement in 8q11-q13 indicate the benign nature of the tumour and prevent the clinician from administering radiation or cytotoxic treatments.

In spindle cell and pleomorphic lipoma, the characteristic chromosome change is loss of material from the region 16q13-qter.

In angiolipoma only normal karyotypes have been found in this typically multifocal adipose tumour. In angiomyolipoma, occurring predominantly in females in the renal capsula or perirenal soft tissue, sporadically or in connection with tuberous sclerosis, again the 12q MAR region is involved in the cases with abnormal karyotype.

Malignant tumours. In the malignant adipose tissue tumours, one type of tumour stands out: the myxoid liposarcoma with its characteristic chromosome change t(12;16). The so-called round cell liposarcoma, a less-differentiated form of myxoid liposarcoma, shows the same translocation and clearly both belong to the same disease entity. This is also confirmed by molecular analysis [38]. At the molecular level, fusion occurs between the *CHOP* gene on 12q13, which belongs to the CCAAT/enhancer binding protein family and is involved in adipocyte differentiation, with the *FUS* (or *TLS*) gene on 16p11, which has an RNA binding domain. The *FUS* gene shows great homology with the *EWS* gene, both in structure and function. It is not surprising, therefore, that the only thus far known case of cytogenetic variant of myxoid liposarcoma involves chromosome 12 with *CHOP*, and not chromosome 16 with *FUS*, but chromosome 22 with the *EWS* gene [36].

Borderline malignancies

Major importance to pathology and the management of the patient is the correct diagnosis in borderline malignant adipose tissue tumours. Pathologists sometimes call these tumours atypical lipoma, especially when superficially located and easily extirpable, and may call them well differentiated liposarcoma when deeply located, for example, retroperitoneally.

Karyotypically, these tumours are characterised by the presence of one extra-ring and/or extra-giant chromosome marker [39]. We propose to call them atypical lipomatous tumours. Molecularly, these rings and giant markers proved to present amplifications of the 12q13-q15 region. Which genes from that region are amplified is not yet totally elucidated, but among the possible and known candidates of *GLI, LRP, CHOP, ATF1, SAS, CDK4* and *MDM2*, the latter three may be particularly involved, but the amplification pattern is not consistent in all tumours.

Summarising the results of this group of adipose tissue tumours as studied by the CHAMP Group, we can state that pathology and genetics, when integrated into a global approach, may greatly contribute to a better diagnosis and

sometimes also to a more adequate and correct therapeutic management of the patient.

CONCLUSIONS AND RECOMMENDATIONS

Recent cytogenetic and molecular genetic investigations in solid tumours in general, and in soft tissue tumours in particular, have provided us with a wealth of information. We have gained new insights into how tumours may arise, and some soft tissue tumours besides their identification by pathology now also have a genetic identity. This genetic identity is defined by specific chromosome changes and by molecular changes related to the chromosome anomalies. Much work, however, remains to be done.

In soft tissues, as in other solid tumours, many tumour types await the first or more extensive chromosome investigation, and in those in which non-random, especially simple chromosome changes emerge, molecular studies are to be undertaken starting from the breakpoints. Those tumours that seem to deviate chromosomally and/or molecularly from the expected, already established genetic changes, must be more thoroughly investigated by both pathologists and geneticists. The same is true for the molecular investigation of chromosomally normal tumours known to show subtypes with specific chromosomal changes, such as lipoma and leiomyoma.

In conclusion, in the management of patients with soft tissue tumours the time has now come to contract a marriage between pathology and genetics. Together, many intellectually exciting subjects can be shared and new horizons can be explored. The ultimate result will be a better care of the patient.

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