REVIEW

The role of microarray technologies in the study of soft tissue tumours

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Array technologies (gene array, tissue microarray and others) are being used in a growing number of research projects involving soft tissue tumours. Gene array techniques allow for measurements of RNA expression levels or gene copy number changes for a large number of genes in a single specimen. A complementary technique, tissue microarrays, allows for the measurement of expression of a single gene in a large number of specimens. These techniques and similar ones have created a fundamentally new approach to the investigation of soft tissue tumours. This review addresses some of the advantages, problems, and solutions to those problems that come with these technologies.

Keywords: gene array, sarcomas, soft tissue tumours, tissue microarray

Abbreviations: aCGH, array comparative genomic hybridization; DFSP, dermatofibrosarcoma protuberans; DTF, desmoid-type fibromatosis; GIST, gastrointestinal stromal tumour; LOH, loss of heterozygosity; MCS, myxoid chondrosarcoma; MFH, malignant fibrous histiocytomas; MPNST, malignant peripheral nerve sheath tumour; SFT, solitary fibrous tumour; SMD, Stanford Microarray Database; TMA, tissue microarray

Introduction

The near simultaneous development of a variety of array-based technologies has provided researchers with global views of tumour biology. These technologies include gene expression profiling, which measures RNA expression, array-based comparative genomic hybridization, which measures genome copy number, and tissue microarrays (TMAs), which can be used to measure DNA, RNA or protein in tumour sections (Figure 1). Other array-based technologies analyse single nucleotide polymorphisms to determine loss of heterozygosity (LOH) or gene copy number changes. The study of soft tissue tumours has been especially amenable to these array technologies, as most soft tissue tumours are relatively homogeneous and are less genetically complex than epithelial tumours. Therefore, the samples have less contamination with non-lesional cells such as fibroblasts or endothelial cells and tumour type comparisons are simpler, with less variation from sample to sample, or even within samples.

One of the major hurdles in this field remains the rarity of soft tissue tumours and the large number of subtypes. Although approximately 15 000 new malignant cases are diagnosed annually in the USA, there are 100 different types of soft tissue tumour that can be recognized by histological examination. Thus, few clinicians and pathologists have extensive experience with any given soft tissue tumour subtype. This situation is further complicated by new modalities of treatment that can be tumour type specific. Despite these obstacles, significant progress has been made in the last few years. An example of this is the gastrointestinal stromal tumour (GIST), a tumour which commonly has activating mutations in KIT or less
commonly in PDGFRA.\textsuperscript{1} With the use of Gleevec, a small molecule inhibitor of these type III receptor tyrosine kinases, three therapeutic categories for GIST can be recognized: tumours that respond to Gleevec therapy, tumours that do not respond, and tumours that develop resistance after initially responding to the drug. Moreover, a number of studies have demonstrated clinicopathological trends associated with the type of mutation in KIT.\textsuperscript{2–4} After initial studies of GIST as a single diagnostic entity,\textsuperscript{5,6} several groups have studied variation in the gene expression profile within this diagnostic entity as it relates to location of the tumour\textsuperscript{7} or the mutations in KIT or PDGFRA.\textsuperscript{7,8} This complexity of data is derived from the study of a tumour only properly recognized as a distinct entity in the past decade! In this review we will cover some aspects of each array technology and their contributions to and potential for soft tissue tumour research.

**Gene array**

Traditional histological and immunohistochemical techniques have had tremendous success in the classification of soft tissue tumours. Early gene array studies quickly established that these established classification schemes correlated extremely well with gene expression patterns. Not surprisingly, tumour types that tightly cluster together by gene expression also tend to be relatively easily classified by histological and immunohistochemical techniques, such as GIST, extraskeletal myxoid chondrosarcoma (MCS) and desmoid-type fibromatosis (DTF, Figure 2). Likewise, tumours

that are difficult to classify or those that are controversial, such as so-called malignant fibrous histiocytomas (MFH) (pleomorphic sarcoma), do not necessarily form clear-cut groups by gene expression. In addition to confirming the classical histological analytical methods of the surgical pathologist, array technologies have yielded a number of new insights, some of which will be discussed below.

The power of gene arrays lies in the ability to position thousands of unique gene sequences with a precisely defined position on a single slide. The total number of spots on a slide (over 40 000 in the case of

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**Figure 2.** Representation of gene expression profiling performed on 156 tumours on cDNA microarrays. Tumours are arranged in columns, while genes are arranged in rows. The intersection between columns and rows is coloured red when a tumour has a relatively high level of expression for a particular gene in a tumour (compared with the expression level in the other tumours used in this analysis). Green indicates a relatively low level of expression. The analysis shows a remarkable clustering of cases with the same diagnosis. For example, all 11 myxoid chondrosarcomas (orange) are clustered in branch 1, all nine cases of GIST (blue) are clustered in branch 2, and all 10 desmoid-type fibromatosis (purple) are clustered on branch 3. On the other hand, not all diagnostic cases show a similar tight clustering pattern; the lesions interpreted as ‘MFH’ (pleomorphic sarcoma, in red) are distributed on a branch that also contains a number of leiomyosarcomas (LMS), malignant peripheral nerve sheath tumours (MPNST), and liposarcomas (LS). Similarly, the four cases of malignant peripheral nerve sheath tumour (green) are scattered over several branches. It should be borne in mind that this is just one type of analysis that is driven in part by the gene filtering used.

AM, Adenomyosis; DFSP, dermatofibrosarcoma protuberans; DSRCT, desmoplastic small round cell tumour; ES, epithelioid sarcoma; ESS, endometrial stromal sarcoma; FH, fibrous histiocytoma; GIST, gastrointestinal stromal tumour; HPC, haemangiopericytoma; LM, leiomyoma; LMS, leiomyosarcoma; LS, liposarcoma; MCS, myxoid chondrosarcoma; MFH, malignant fibrous histiocytoma (pleomorphic sarcoma); MLS, myxoid liposarcoma; MPNST, malignant peripheral nerve sheath tumour; MyxoFS, myxoid fibrosarcoma; Neur, neurofibroma; NF, nodular fasciitis; RMS, rhabdomyosarcoma; SCHW, schwannoma; SFT, solitary fibrous tumour; SS, synovial sarcoma.
cDNA arrays, more in the case of oligonucleotide arrays) exceeds estimates for the total number of genes in the human genome. This allows for global gene expression profiling. A variety of commercial and non-commercial platforms can be used to perform global gene expression profiling. These include spotted cDNA arrays such as those generated at the Stanford Functional Genomics Facility (http://www.microarray.org/sfgf/jsp/home.jsp), or at Agilent, or the Affymetrix oligonucleotide-based arrays. Initially it was thought that studies performed on different platforms were difficult to compare, but recent studies, performed with standardized data analysis and sample preparation, show that, in fact, a remarkable similarity between data obtained from different laboratories and performed on different platforms can exist. However, a variety of other parameters influence the data generated, including, but not limited to, the method of RNA isolation and purification from the samples to be analysed (including amplification), the type of reference sample used, and the type of gene sequence that is spotted or synthesized on the array (cDNA versus oligonucleotide). These variables concern only the quality of the raw data. A myriad of further decisions remain as to the filtering and selection of data to be ultimately analysed. Filtering of data is necessary to remove genes that are poorly measured, e.g. those gene spots that reside in areas where the local background of the gene chip is very high. Further filtering usually removes those genes that are not of interest because they do not vary significantly from expression levels in the samples used for the study. Another major variable is the selection of cases used for the analysis. As shown in Figure 3, inclusion of additional cases to a study can highlight initially unrecognized genes. Gene expression profiling usually looks at variation in levels of mRNA for many genes between different tumours. The data obtained are dependent on the number and types of sarcomas that are investigated. For example, in Figure 3A, where specimens of solitary fibrous tumours (SFTs) are compared with desmoid-type fibromatosis, it would appear that there are only genes that are either expressed in SFTs but not in desmoid-type fibromatosis or vice versa. This is due to the fact that the genes shown were selected based on variation in expression levels in the samples tested (irrespective of diagnosis). However, when other sarcoma specimens are added to the comparison (Figure 3B), it becomes clear that there is a significant number of genes that are expressed in both SFTs and DFT but that are not found in, for example, GISTs, synovial sarcoma...etc. Therefore the selection of sarcomas that are analysed within an experiment strongly influences the genes that pass through filtering.

Gene array analysis generates a tremendous amount of raw data. A recent analysis by Michiels et al., for example, showed that gene sets published by different groups as prognostically significant in breast carcinoma had very little overlap. More worrisome was the finding that these gene sets were not very robust in several studies and that the composition of these gene sets could vary significantly depending on the analysis used. One of the reasons for this lack of ‘repeatability’ could be that many studies use the same set of cases for both gene discovery and validation. This procedure can cause ‘overfitting’ of data. It is for this reason that confirmation of gene array data on a separate set of patients can be extremely valuable. TMAs developed by the groups of Kalionemi and Sauter form an excellent method for such validation studies (see below). Despite these concerns, when the overall biology is considered, a significant correlation between different gene array studies can become apparent by simply comparing the data from a variety of sources. For instance, the expression of genes involved in retinoic acid response in synovial sarcoma was noted in four of five expression profiling studies that used different platforms and different combinations of tumours. At an informatic level, however, the ‘manual’ comparison of data published by different groups is extremely laborious, and it is likely that many interesting correlates will be missed. The Stanford Microarray Database (SMD) (http://genome-www5.stanford.edu/) has been created as a resource for the research community in the storage of microarray data published by SMD users and, by disseminating its source code, outside users. The database can handle a variety of data from Affymetrix GeneChips, Agilent Catalogue or Custom arrays or data created by
SpotReader (Niles Scientific, Portola Valley, CA, USA). One group has also attempted to address the standards for presenting and exchanging gene array data. The Minimum Information About a Microarray Experiment (MIAME) outlines the minimum information required to ensure that microarray data can be easily manipulated between research groups. Databases such as these (and others such as http://research.nhgri.nih.gov/microarray/) are an excellent source of potential new markers that can be validated by others in TMA studies.

Figure 3. Gene expression profiling data obtained from two tumours (solitary fibrous tumour and desmoid type fibromatosis) (A) highlights genes that vary between these two lesions only. Inclusion of other sarcomas (B) shows genes that show shared expression in the two tumours (white ellipses).
The initial aim of many of the early projects on gene expression analysis of soft tissue tumours was to characterize these neoplasms at a molecular level and to do a genome-wide search for new diagnostic markers. In our initial paper\(^6\) we generated the gene-expression patterns of 41 soft tissue tumours using cDNA microarrays. We found that synovial sarcomas, GISTs, neural tumours and a subset of the leiomyosarcomas showed quite distinct gene expression patterns. Mirroring this finding, a second subset of leiomyosarcomas was indistinguishable from MFH/pleomorphic sarcomas. Segal et al. also conducted a general survey of conventional fibrosarcoma, leiomyosarcoma, round-cell liposarcoma, pleomorphic liposarcoma, de-differentiated liposarcoma, clear-cell sarcoma, synovial sarcoma and GIST.\(^{16}\) They likewise found that some of these tumours displayed remarkably distinct and homogeneous gene expression profiles. Strikingly, both studies found that the more pleomorphic tumours (such as MFH and a subset of leiomyosarcomas) were heterogeneous, did not cluster together well and were not defined by a distinct gene expression profile of highly expressed genes, except for cell cycle genes. This behaviour of pleomorphic sarcomas was also seen by Lee et al.,\(^{14}\) who evaluated the gene expression patterns for synovial sarcomas, leiomyosarcomas and MFHs. They found good clustering of eight of nine synovial sarcomas. However, leiomyosarcomas and MFHs could not be distinguished by hierarchical clustering analysis. The authors concluded that sarcomas conventionally defined as MFHs do not represent a separate diagnostic category. However, these studies were performed on a relatively small number of cases and more specimens may need to be analysed before MFH can be discarded as a diagnostic entity.

After these initial studies in which low numbers of cases with a specific diagnosis were analysed, subsequent studies started to use larger numbers of cases with a specific diagnosis in an attempt to find new subtypes of tumours within those diagnostic groups. In a study by Quade et al.,\(^{21}\) an expression profile was generated for uterine smooth muscle tumours. Their analysis was able to distinguish benign and malignant samples, myometrium and leiomyoma. Interestingly down-regulation of specific genes in uterine leiomyosarcoma was the most common pattern of differential gene expression (selected by the three-way ANOVA).

Others have also examined leiomyosarcomas and found encouraging differences. Lee et al. looked at the gene expression signature of leiomyosarcomas as a model for identifying tumours that will undergo metastasis.\(^{22}\) Skubitz and Skubitz looked at the differences between leiomyosarcomas, leiomyomas and uterine smooth muscle.\(^{23,24}\) Ren et al.\(^{25}\) analysed 11 cases of leiomyosarcomas of different histological grades against other soft tissue tumours. These authors found gene expression patterns that enabled them to subclassify the leiomyosarcomas into three groups. Ninety-two genes correlated well with tumour differentiation and clinical aggressiveness. However, these studies still used relatively low numbers of cases and it is possible that, in these studies, overfitting of data may have occurred that led to apparent correlations between clinicopathological features and gene expression patterns. Larger studies may be necessary to exclude this potential overfitting problem. In one such study, Watson et al.\(^{26}\) examined 25 NF1-associated and 17 sporadic malignant peripheral nerve sheath tumours (MPNSTs) and were unable to identify a molecular signature that could reliably distinguish between these two tumour types in independent training and test sample sets. However, they did find a small subset of tumours that had increased expression of genes associated with neuroglial differentiation and relative down-regulation of proliferation and growth factor-associated transcripts.

The manuscripts described above are examples of studies which were intended to find gene expression profiles that distinguished different tumour subgroups and/or to identify clinically relevant subtypes of a particular tumour group. Of course, gene expression profiling also leads to the identification of new and diagnostically relevant markers. A number of diagnostic markers have been discovered by this type analysis. These include Apo D,\(^{27}\) DOG1\(^{28}\) and PKC theta.\(^{29,30}\) One example is the identification of DOG1 as a novel marker in GIST. A subset of GIST do not have mutations in the KIT gene, but rather in PDGFRA, and often fail to react for KIT antibodies by immunohistochemistry.\(^{31}\) In this case, such tumours may be misdiagnosed as leiomyosarcoma or fibromatosis. Based on gene microarray findings, DOG1 (TME16A) was identified as being expressed on most GISTs, including those that harbour the PDGFRa mutation. This observation was validated and extended to a much larger set of tumours using a polyclonal antibody and TMAs of archived formalin-fixed paraffin-embedded tissue.\(^{28}\)

By looking at gene expression profiles, one can also identify potential therapeutic targets that are expressed at particularly high levels in one tumour type over another. For example, microarray expression profiling has shown higher ERBB2 (her2/neu) and EGFR expression in synovial sarcoma compared with other soft tissue sarcomas.\(^{6,13,32}\) Based on the finding of high levels of EGFR in synovial sarcoma, an EORTC protocol...
(62022) was started to test the efficacy of Iressa treatment in synovial sarcoma patients. Likewise, the recognition of high levels of expression of ERBB2 may lead to trial involving trastuzumab therapy for this tumour. A more recent paper described how expression profiling led to the discovery of a novel potential therapeutic target, FZD10, for synovial sarcoma.33

Gene microarray analysis can also be used to ask more complex biological questions. For example, Mintz et al. attempted to identify factors that would predict response to chemotherapy in osteosarcoma.34 The authors examined 30 osteosarcomas, 15 with limited necrosis and 15 with extensive necrosis following induction chemotherapy. Markers for poor responders with limited necrosis were gene products involved in extracellular matrix remodelling and osteoclast differentiation. In a separate paper from the Triche group,35 the EWS-FLI1 fusion was examined for its influence on the primitive neuroectodermal phenotype of the Ewing’s sarcoma. The authors established a tetra-cycline-inducible EWS-FLI1 expression system in a rhabdomyosarcoma cell line and looked for changes in cell morphology and expression following induction of EWS-FLI1 expression. This study suggested that phenotype of Ewing’s sarcomas is attributable to the EWS-FLI1 expression and the resultant phenotype resembles developing neural crest. Gene expression studies have even shown that they can be used to correct ‘missed diagnoses’. This includes distinguishing fibrous histiocytoma from dermatofibrosarcoma protuberans (DFSP)36 and rhabdomyosarcoma from leukaemia.37 However, due to costs, complexity of technique and other reasons, it will possibly be some time before gene arrays are used as an adjuvant diagnostic tool in the clinic.

These initial soft tissue tumour expression profiles can almost be seen as ‘proof of principle’ experiments that carry a lot of promise for future studies. However, when we compare the progress of soft tissue tumour analysis by gene array analysis with more prevalent tumours, such as breast cancer, it is clear that the soft tissue studies lack very large datasets with clinical outcome data. The development of these datasets will take time and will require a major collaborative effort between many groups.

**Array comparative genomic hybridization**

In array comparative genomic hybridization (aCGH) the copy number for thousands of genes is determined in a manner similar to that used to look at mRNA levels. cDNA arrays (the same as those used for gene expression profiling) can also be used for aCGH, when the material applied to the arrays consists of fluorescently labelled DNA rather than cDNA. In the past there was concern that cDNA microarrays or oligonucleotide microarrays contained DNA fragments that were too short for aCGH experiments. Another concern was that, while gene amplification could be identified, gene loss would not be detectable. However, in a prior study the group led by Pollack was able to distinguish normal females from individuals with loss of 1 copy of chromosome X (XO).38,39 Other data from the Pollack laboratory show that while a single isolated gene loss may not be detectable, single copy number changes can be detected in specimens that contain 50% breast tumour (admixed with stroma) in regions where at least five adjacent genes are affected. Since soft tissue tumours contain little ‘contaminating’ stroma, we can expect an even greater degree of sensitivity with this technique. Other groups are now also reporting success using cDNA arrays for aCGH40 and some even report success for oligonucleotide arrays.41

aCGH is so far a relatively underutilized tool for sarcoma research. The main advantage of aCGH is that the queried molecule, DNA, is reasonably preserved in formalin-fixed paraffin-embedded block. This feature helps researchers overcome a major hurdle in soft tissue tumour research: the scarcity of fresh frozen samples. Paraffin-embedded archived tissue also allows projects to associate outcome data with genomic changes. We have studied paraffin-embedded samples up to 10 years old with very good results.36,42

**Tissue microarray**

TMAs are an excellent complement for gene arrays (Figure 1). Whereas gene arrays generate thousands of gene expression data points for a single tumour on a single slide, TMA analysis generates hundreds of tumour expression data points for a single gene on a single paraffin block. Enormous numbers of cases can be obtained. For example, in collaboration with several other institutions, we have generated soft tissue tumour TMA with over 500 cases representing 55 diagnostic classes. Any promising new marker that is identified can now be quickly analysed for its reaction pattern across a wide variety of sarcomas, resulting in a much more complete first characterization than would be practical using conventional tissue sections.

A second facet of TMAs is that the expression data are multidimensional: not only does they generate a measurement of relative expression but they also determine cellular, and to a limited extent subcellular, tissue localization. Virchow’s dogma ‘Omnis cellula e cellula (Every cell from a cell)’ is still central to our
thinking in carcinogenesis and TMAs directly address this point. This multidimensionality creates unique problems in reporting the data from a TMA in a simple table, as each core of tissue within the TMA may have multiple cell types. For cancers, this includes the neoplastic cells, stromal cells, vascular cells, inflammatory cells, etc. Thus the number of entities within a single core that can be measured may be many more than just one. Sarcomas tend to have a morphologically less complex microenvironment than carcinomas, but the nature of inflammatory cells and non-neoplastic stromal cells in sarcomas has not been well studied to date. The multidimensional aspect of histological interpretation and the vast numbers of specimens represented in these TMAs necessitate a solid database to archive staining results and interpretations.

In almost every TMA study, the question arises whether the core sample on the TMA is representative of the entire lesion; this issue can be minor for diffuse processes but critical for focal processes. By and large, soft tissue tumours are relatively homogeneous and do not suffer as much from these problems. A second problem is the standardization of scoring. Most published TMA datasets have been scored manually. This creates problems with reproducibility, typically creates a bottleneck in data generation at the scoring step, and makes the data only semiquantitative. A great deal of effort is made to make the scoring of TMA data more objective and it can be expected that TMA scoring for some markers could be automated more and more in the future. A third hurdle is the quality of the tissue arrayed. Careful selection of cases with well-preserved blocks and attention to the site at which the core is taken prevent a number of problems. Fixation issues are probably the biggest problem that is not easily controlled, especially if the cases are rare and are derived from a number of outside hospitals (as is often the case with soft tissue tumours). The effects of variable fixation on immunohistochemistry have been well studied but no comment was made on in situ hybridization. Variability in fixation results in variability in signal. This variability is difficult to measure and account for in analysis. One method we have used is to examine the quality of tissue mRNA by testing for the reactivity with an Oligo dT probe; cores that fail to react are thought to have compromised quality of the mRNA and are excluded from further interpretation.

TMAs have typically arrayed tissues prepared in an almost identical fashion, such as paraffin-embedded blocks from surgical pathology material. However, a wide variety of samples can be incorporated into a TMA block, including cell culture pellets. We recently combined traditional cored samples with embedded tissue to maintain the correct orientation of certain tissue, such as skin, and to determine the expression pattern within a complex tissue architecture (Figure 4).

Use of soft tissue tumour gene expression profiles to characterize normal stromal cell subtypes

We have recently used soft tissue tumour gene expression patterns to help define normal stromal cell counterparts. Measurement of the global expression pattern of a stromal cell can be difficult. Presumed subtypes of fibroblasts cannot be distinguished by histological means and only very few markers are available that positively identify these cells. Moreover, they are difficult to purify. Previous expression profiling studies had shown remarkable differences in expression profiles between cultured fibroblasts isolated from different sites and have shown that fibroblasts in culture, upon exposure to serum, exhibit a gene
expression profile that shows similarity to that seen in wound healing. The expression of this profile in some breast carcinomas correlated with clinical outcome. These studies clearly indicated a remarkable biological function for these bland-appearing cells. Expression patterns among fibroblasts in tumours or reactive conditions are difficult to study directly due to tissue heterogeneity. Excluding epithelial structures, there are a considerable number of other cells that comprise the microenvironment, including vascular structures and inflammatory cells. Moreover, the diversity of fibroblastic and myofibroblastic cells that may be present adds an additional layer of complexity. The gene expression profile of a soft tissue tumour represents primarily a single cell type because the majority of the cells in the lesion are tumour cells. To a degree, many soft tissue tumours recapitulate normal tissue components both morphologically and by protein expression, and this is the basis for much diagnostic nomenclature in surgical pathology. We hypothesized that tumours with different fibroblastic phenotypes might represent different activation states or different subtypes of normal fibroblasts or stromal cells and we decided to study two bland fibroblastic tumours, SFT and DTF. The histological growth patterns are distinct, but the spindled cells that comprise these tumours are cytologically very similar and hard to distinguish. Thus, these two tumours form a good model system to use for discovery of novel connective tissue markers. We found that the gene expression patterns of these two tumours are distinguished by differences in expression of a variety of functional groups of genes: DTF expresses a fibroctic response and SFT tumours express genes that are typically found in the basement membrane. By immunohistochemistry and *in situ* hybridization, markers representative of the separate DTF and SFT gene sets highlighted at least two groups of normal connective tissue ‘fibroblasts’ or stromal cells. The cells positive for DTF markers are found in a variety of reactive tissues ranging from inflammatory granulation tissue to scar tissue. In contrast, cells positive for SFT markers tend to be found in normal tissue. The stromal cells surrounding breast lobules and eccrine lobules of the skin were strongly reactive for SFT markers and negative for DTF genes. Furthermore, analysis of the gene expression signatures of these soft tissue tumours in a breast carcinoma expression dataset has suggested that there may be molecularly distinct patterns of stromal reaction in breast cancer. These stromal reaction patterns appear to be correlated with differences in the biology of the tumours that are reflected in clinical outcome. We hope that the study of additional soft tissue tumours such as low-grade fibromyxoid sarcoma (in collaboration with Dr C. Antonescu) will lead to the discovery of additional fibroblast markers. In this way, the study of soft tissue tumours may lead to a functional classification of fibroblasts, similar to the way in which the study of lymphomas led to the recognition of functional subsets of lymphocytes.

**Conclusion**

Gene array technologies now present a novel viewpoint of global expression profiling and high throughput analysis. No doubt, the current research using these technologies is the first iteration of many. For example, new gene arrays measure splicing variants and future tissue arrays could contain thousands of cases in order to capture information on rare subtypes.

**Note added in proof**

Recently, a paper by Baird *et al.* appeared which described the gene expression profiling of 181 bone and soft tissue sarcomas (*Cancer Research* 2005; 65: 9226–9235).

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