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Review

Transcription Factors as Drug Targets in Cancer

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Within multicellular organisms, cells are continually signalling to each other to keep in tune with their environment. The ultimate targets for the majority of these signal pathways are upstream transcription factors, whose activity is thereby modulated, resulting in a new pattern of gene expression suitably coupled to the needs of the cell. It has been estimated that up to 10% of human genes may encode transcription factors, thus emphasising how fundamental the control of gene expression is to the processes of cellular division and differentiation during normal development. As a corollary of this, transcriptional regulation can also profoundly affect the course of growth-related diseases such as cancer. Of course it has been realised for some time that the normal counterparts of many oncogenes are transcription factors whose proper role is in the control of normal cell growth. More recent work has begun to identify several other transcription factors which may play a role in cancer, and strategies are now being developed which are designed to use our growing knowledge of transcriptional control mechanisms in the development of novel cancer therapies.

Key words: transcription factors, cancer therapy

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HOW IS TRANSCRIPTION REGULATED?

BEFORE A mature mRNA molecule reaches the cytoplasm of the cell to be translated into protein, a number of highly regulated processes must have taken place: transcription initiation, elongation, termination, splicing, polyadenylation and nuclear export. The most tightly controlled of all of these, and hence the rate determining step for most genes, is that of initiation where the DNA sequences around the start of the gene are recognised by a number of nuclear proteins termed transcription factors. These transcription factors can be divided operationally into two groups. The first group consists of a series of 20–30 proteins, found in all cells, which complex with RNA polymerase II (Pol II, itself a multiprotein complex termed the holoenzyme) at the transcription start site. The role of these factors is to recognise and bind to gene promoters and subsequently position the Pol II holoenzyme accurately at the start of the gene (see Figure 1). They are collectively termed the 'basal machinery' or 'general transcription factors' (GTFs) [1]. As the name implies, these proteins are required for the initiation of transcription of all protein-encoding genes and consequently they cannot be considered as tumour-specific targets.

The second group of transcription factors are more gene- and cell-specific; for example, although many of these proteins are also ubiquitous, they may be active only at particular points within the cell cycle [2], while others may only be synthesised within defined cell types at certain stages in development [3]. These proteins generally have two main functional domains. One domain specifically recognises and binds to DNA sequences within the gene regulatory elements, while the second interacts with the basal machinery to regulate the efficiency of transcription initiation. Thus, these so-called 'upstream' factors can either stimulate transcription initiation (activating factors) [4, 5] or interfere with this process (repressors) [6] depending on the nature of their interactions with the general factors (see Figure 1). Thus, activators increase the chances of transcription initiation by encouraging the binding of Pol II holoenzyme through interactions with their activation domain, while repressors act via their repression domain to destabilise complex formation at the start site, making transcription initiation less likely. Interactions between some upstream factors and the general machinery may also be ensured

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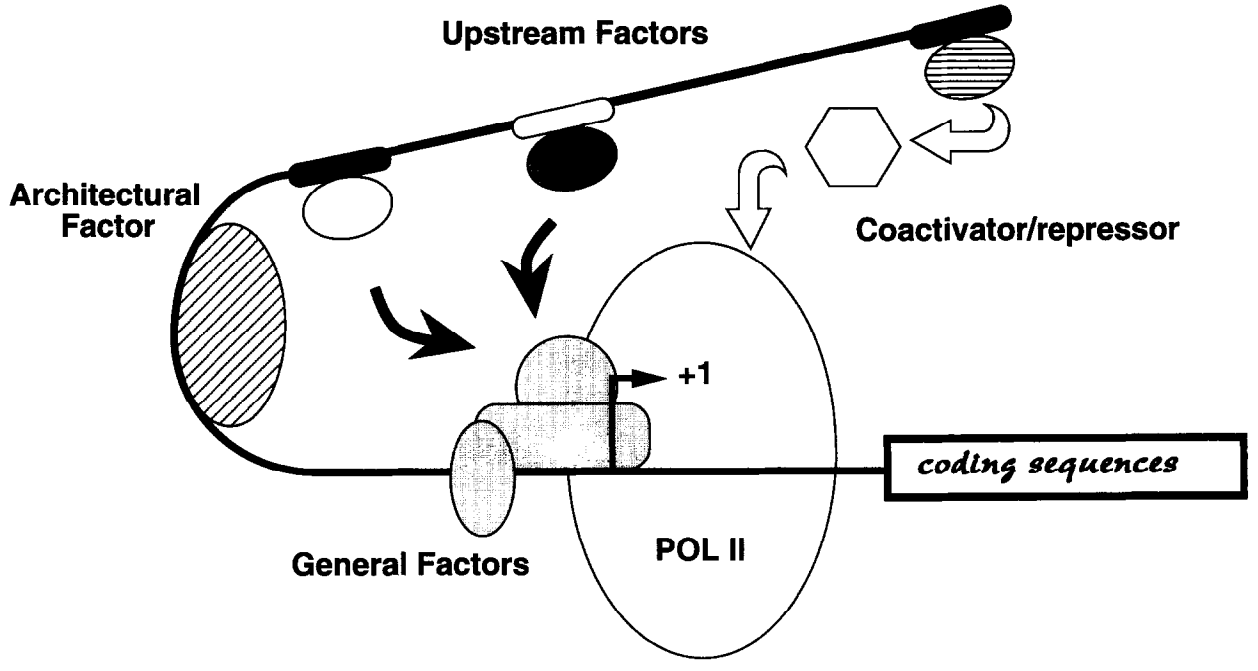

Figure 1. Assembly of transcription initiation complexes. The first base of a gene that is copied into RNA, designated +1, is shown as an arrow just upstream of the gene coding sequences. The DNA sequences in the vicinity of this first base (the proximal promoter) are bound by the general transcription factors (GTFs) leading to the recruitment of the Pol II holoenzyme to the gene. The efficiency with which the GTFs recognise/bind to a particular promoter is influenced by the presence of upstream factors. These specifically bind to sequences within promoter/enhancer regions of the gene through their DNA binding domains (shown as black and white rectangular objects). Subsequent to binding, the upstream factors can either enhance (activators) or discourage (repressors) the binding of the GTFs through protein–protein interactions via their transcription modulation domains (shown as ovals). These interactions may be direct (curved black arrows) or via coactivators/corepressors (curved white arrows). For the protein–protein interactions to occur, the promoter DNA must be kinked or bent. This can be achieved in part by the binding of the GTFs and the upstream factors themselves, in combination with the chromatin-forming proteins or, as shown here, specific architectural transcription factors may also help to stabilise a bend in the DNA.

via non-DNA binding co-activators [4, 7] or co-repressors [1, 6] which can also be specific to certain transcription factors or promoters (see Figure 1). The activity of many upstream factors can also be regulated, for example by post-translational modifications such as phosphorylation, or the binding of ligands and it is through this modulation of activity that the pattern of gene expression is suitably coupled to the needs of the cell, based on the signals to grow or differentiate that are received at the cell surface [5, 8]. The more 'gene-specific' nature of these proteins means that the expression of certain genes may be downregulated by targeting particular upstream factors.

The binding sites for upstream factors often lie close to the gene transcription start site, in a region termed the gene promoter, but many important regulatory sites are also found within enhancer/silencer regions several kilobases up- or downstream of this. As illustrated in Figure 1, for the upstream factors to interact efficiently with the basic machinery, it is envisaged that the DNA must be bent to allow productive protein–protein interactions to occur [9]. Of course, all nuclear DNA is packaged into higher order structures through the binding of histones to form chromatin, but the precise architecture of these structures is thought to be quite distinct in transcriptionally active regions of the genome. Thus, transcriptionally active chromatin is thought to be more 'open' allowing easier passage of Pol II, and both general and gene-specific transcription factors are thought to contribute to this local reorganisation of chromatin which can lead to the establishment of patterns of gene expression that are stable through several rounds of cellular division [10–12]. The relative stiffness of short DNA segments (up bp 500 bp) means that even in the promoter region, bending or kinking of the DNA is required to bring factors into close proximity. This may occur through the binding of general chromatin proteins such as the high mobility group (HMG) proteins, but may also be achieved by the interaction of gene-specific architectural factors (see Figure 1; [13]), or by the DNA binding of certain upstream factors and GTFs [14]. Much less is currently known about how many of these latter factors work, but it is likely that they may prove to be useful targets in the future. For example, the bent DNA structures caused by the anticancer drug, cisplatin, are specifically recognised by the protein HMG1 and this has been shown to contribute to drug efficacy by preventing recognition of the modified DNA by the cellular repair machinery [15]. It is hoped that new anti-tumour drugs may be designed based on structural studies looking in detail at these interactions [16].

HOW CAN WE INTERFERE WITH TRANSCRIPTION FACTOR ACTIVITY?

With our current level of knowledge, therefore, the most accessible group of transcription factors that may be targeted to specifically alter gene expression in tumour cells are the upstream factors. Figure 2 illustrates possible steps in the 'life cycle' of such a protein from its synthesis in the cytoplasm to its DNA bound state within the regulatory regions of a gene whose expression it controls. Depending

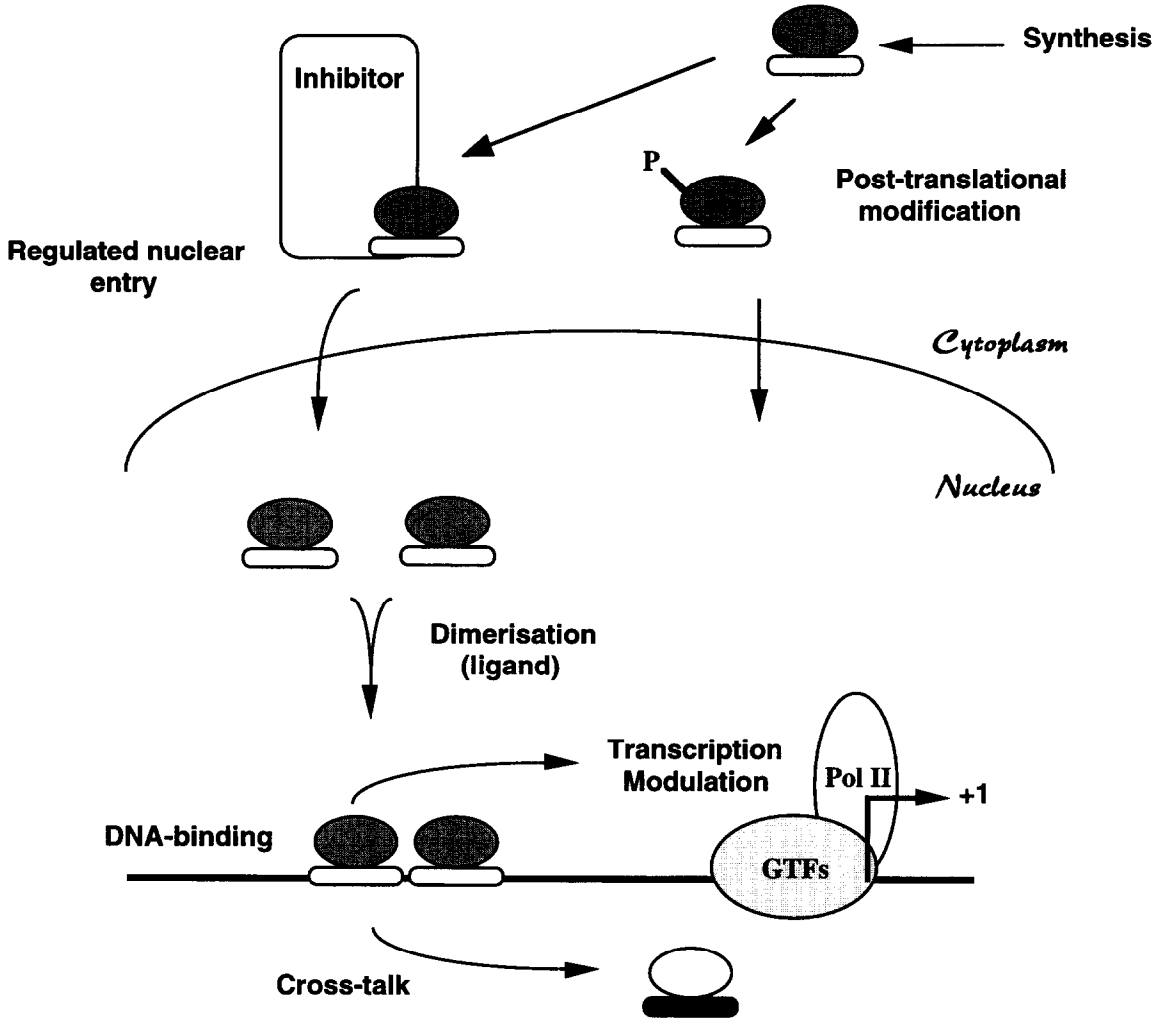

Figure 2. Potential sites for pharmacological intervention in transcription factor function. No two factors are regulated in exactly the same way, but this figure aims to give a flavour of some of the stages in the 'life' of an upstream factor that may be considered when attempting to design specific transcriptional inhibitors. After being synthesised, most upstream factors translocate directly to the nucleus, but some are sequestered in the cytoplasm bound to an inhibitor protein until released on receipt of an appropriate signal. Cellular signalling can also lead to the post-translational modification of some factors, for example, by phosphorylation, which leads to a modulation in their activity. Many factors bind DNA as dimers or multiprotein complexes, and this can be regulated by phosphorylation or ligand binding. Once bound to DNA, the upstream factor needs to interact with the basal machinery and possibly with other proteins such as cofactors or other upstream factors (cross-talk).

on the factor, a number of sites for potential pharmacological intervention are apparent. As mentioned above, many factors are modulated via phosphorylation [17], so their activity may be altered by targeting certain kinases or phosphatases. Some transcription factors are regulated at the level of nuclear entry. The classic example is NFκB, a factor involved in the control of expression of inflammatory response genes, which is held in the cytoplasm in a complex with its inhibitor, IκB. A number of stimulants, including phorbol esters and dsRNA, can inactivate this complex, allowing NFκB to translocate to the nucleus. The anti-inflammatory action of aspirin has been explained recently by showing that it acts to maintain the IκB/NFκB complex, thus NFκB is unable to translocate to the nucleus and activation of the inflammatory response genes is thereby prevented [18]. The molecular events involved are distinct, but the same overall pathway also explains the action of the immunosuppressive drug cyclosporin which prevents nuclear entry of the NF-AT upstream factor required for expression of the interleukin-2 gene during T-cell activation [19]. Many upstream factors need to bind DNA as dimers—either as homodimers or as heterodimers with another protein. Thus, the oncoprotein Fos can only bind DNA when dimerised with Jun to form a protein complex often referred to as AP1. Other factors require ligand binding for full biological activity, for example the nuclear factor superfamily which includes the retinoic acid receptors and steroid receptors such as the oestrogen receptor. Ligand binding generally controls dimerisation and DNA binding, but the precise role is subtly different for each family member; for example, ligand binding is also coupled to nuclear translocation for the oestrogen receptor [20].

The most attractive targets for interfering with transcription factor activity are either the DNA binding or the transcriptional modulation activities as these domains constitute the specific active surfaces of these proteins. The majority of

upstream factors can be classified into one of several large families by the type of DNA binding domain structure they possess and whether it binds DNA as a monomer or needs to dimerise, either with itself or another family member. Examples of the more common families are listed in Table 1. The three-dimensional structures of many transcription factor DNA binding domains have now been solved by X-ray crystallography. This obviously provides a great deal of information which, in the future, may be put to use in the rational design of interfering agents such as peptide mimetics. These could be powerful tools to disrupt not just DNA binding, but also the interaction of the activation/repression domains with the basal machinery. Currently, such approaches are in their infancy and one major problem is that, although the DNA binding domains alone have been relatively straightforward to crystallise, this has not so far proved possible for the more disordered transcription activation domains, and hence there are no complete three-dimensional structures for any of these upstream factors. Consequently, to date, the majority of schemes to antagonise transcription factor function have concentrated on disrupting specific DNA binding through targeting the DNA binding site itself. Clearly, many current drugs, particularly intercalating agents, are used to target DNA in a general sense, but if specific DNA sequences could be targeted then it should be possible to disrupt the binding of an upstream factor to a particular gene. In this context, it should be remembered that while upstream factors recognise specific DNA binding sites, in practice there is a certain amount of degeneracy in the sequences bound, and it may be possible to inhibit factor binding at one (or a few) of its cognate genes without completely inhibiting all binding by that factor. One approach has been to modify chemically non-specific DNA binding compounds to try to produce molecules that only bind defined DNA sequences. For example, the AT-rich binding preference of the naturally occurring oligopeptide, distamycin, can be altered by adding imidazole groups and then multimerising the monomers to produce molecules with binding specificity to extended DNA sequences [21, 22]. These compounds bind in the minor groove of DNA and can be conjugated with DNA alkylating or crosslinking agents (such as psoralen) to modify permanently the DNA at that site [23].

Another technology that has been used to bring damaging agents to particular DNA sequences is that of triplex DNA. Here, short oligonucleotides are designed to bind within the major groove of the DNA duplex thus producing a triple helix structure [24]. When first discovered, triplex formation was found to be very specific for sequences containing polypurine/polypyrimidine runs. However, the use of modified bases has greatly expanded the range of sequences that can be specifically targeted by these molecules, and a number of reports have appeared where triplex oligonucleotides have been used to downregulate the promoters of cancer-associated genes [25, 26]. Other groups have sought to increase the stability of the triplex structures by using oligomers of polyamide nucleic acid (PNA) where the deoxyribose phosphate backbone of DNA is replaced with polyamide linkages as found between amino acids in proteins [27]. However, perhaps the most obvious way to target transcription factor binding is to introduce into the cell an excess of binding sites in the form of double-stranded oligonucleotides to remove competitively the cognate factor off its sites of action within the nucleus. One report using this approach has appeared [28], but the major problem with all of these methods is ensuring that physiologically useful amounts of these molecules enter the cell.

Because of these problems, the majority of pharmaceutical companies seeking to develop antitranscription reagents are still wedded to the time-honoured approach of identifying either natural or synthetic small molecules that should readily diffuse into cells. This requires a rapid, cell-based or *in vitro* assay which can be adapted for use with high throughput screens (often performed using robotics) to screen 'libraries' of synthetic and naturally occurring compounds. The key to success lies in the robustness of the assay and the ability to eradicate rapidly false positives by using appropriate controls. As transcription assays (mainly based on the bacterial enzyme chloramphenicol acetyl transferase, CAT) have been used by the research community for nearly two decades, this is actually not a problem. The obvious advantage of this approach is that it requires virtually no information about the structure or the mode of regulation of the upstream factor of interest, and a chemical that acts at any of the control points in Figure 2 has the potential to be a useful drug as long as it is reasonably specific. The major decision, therefore, is which gene or transcription factor should be targeted to develop a novel anticancer agent?

Table 1. Examples of major families of upstream transcription factors

Family	Example	Binding form
Zinc finger	Oestrogen receptor	Homodimer
	Retinoic acid receptors	Homo- and heterodimers
bZIP	Fos family	Heterodimers
	Jun family	Homo- and heterodimers
bHLH	Myc family	Homo- and heterodimers
Ets complexes factors (winged HTH)	Ets family	Monomers; ternary complexes with other factors
Rel (beta barrel)	NFκB	Homo- and heterodimers
Homeodomain (HTH)	Hox factors	Monomers

All of these families are known by the name given to the homologous domain which they all contain and which has now been shown in each case, from X-ray crystallography data, to comprise the DNA binding (and dimerisation) domain of the protein. Proteins in some of the families contain additional homologous regions associated with other functions; binding of the IκB inhibitor in the Rel factors, for example. bZIP, basic domain/leucine zipper; bHLH, basic domain/helix loop helix; HTH, helix turn helix.

WHICH TRANSCRIPTION FACTORS WOULD MAKE NOVEL TARGETS FOR CANCER TREATMENT?

As mentioned above, there are already drugs used in clinical practice which specifically target upstream transcription factors, namely aspirin in inflammatory disease and cyclosporin for the immunosuppression of transplant patients.

Another existing antitranscription agent is of course tamoxifen, one of the most important drugs in the treatment of breast cancer. Tamoxifen binds to the oestrogen receptor in place of oestrogen and, although the receptor can still dimerise and bind to gene promoter/enhancer regions, it is now a poor transcriptional activator. This is because the tamoxifen-bound receptor does not have a properly folded C-terminal transcription acvtivation domain and, therefore, fails to interact productively with the basal machinery. However, tamoxifen is only a partial oestrogen agonist as the receptor is still capable of some transcriptional activation through a ligand-independent N-terminal activation domain. As this activity has been thought to contribute to the failure of tamoxifen therapy in some patients, newer anti-oestrogen drugs are being developed. These compounds generally prevent receptor dimerisation and hence DNA binding and are, therefore, complete antagonists [29]. Modified ligands for other members of the nuclear receptor family may also be used in cancer treatment in the near future. Although initially thought to act as completely independent upstream factors, it has become increasingly clear that the nuclear receptors also act to modulate the activity of other upstream factors, in particular the Fos/Jun AP1 complexes. This interaction has acquired the term 'cross talk' (see Figure 2 [19]) and takes the form of mutual transrepression such that non-DNA bound nuclear receptors, particularly retinoic acid receptors (RARs), can repress the activity of DNA-bound AP1, and vice versa. For the cross-talk interactions to occur, the RARs must bind ligand. The major interest in these interactions comes about as AP1 activity is linked to cell proliferation and the induction of genes involved in tumour metastases, processes which can be ablated by administration of retinoids. The clinical usefulness of retinoids is limited due to side-affects associated with transcriptional activation by the RARs when bound to their cognate binding sites. However, several groups have now shown that it is possible to uncouple these two receptor activities by selecting synthetic retinoids which fail to activate transcription, but will still inhibit tumour cell proliferation through RAR repression of AP1 activity [30–32].

Retinoids have already been used extensively in the treatment of acute promyelocytic leukaemia (APL), a disease characterised by the failure of promyelocytes to differentiate to mature forms. The cells, therefore, remain in the proliferative compartment, but can be induced to differentiate with retinoic acid, frequently leading to complete remission [33]. APL is characterised by a translocation between chromosomes 15 and 17 which is observed in nearly all patients. Genetic analysis of these translocations has shown that they always result in the fusion of the 5′ portion of the PML gene to the gene for one of the retinoic acid receptor genes, RARα. This gene fusion results in the production within the leukaemic cells of a chimeric protein with a portion of the PML protein fused to RARα. PML is a myeloid specific protein which itself resembles a transcription factor and the inference is that these additional sequences on the RARα protein inhibit its normal role in the differentiation of promyelocytes, but that this can be partially restored by the ectopic administration of retinoic acid [34]. Surprisingly, this type of translocation, resulting in the formation of a chimeric transcription factor, occurs in a number of other human tumours, particularly haematological malignancies and soft tissue sarcomas [35]. Due to the modular nature of transcription factor structure, these chimeric proteins often have the DNA binding domain of one factor fused to the transcription modulation domain of another (see Table 2 for examples). The hybrid factors, therefore, possess novel activities and, by either interfering with normal endogenous factors or inappropriately activating/repressing developmentally important genes, they are able to alter profoundly the normal differentiation programme of the cells expressing them. This underlines the important role transcription factors normally play in development and morphogenesis. Being unique to the tumour cells, these chimeric factors make ideal candidates to be put through the high throughput screens described above to find novel small molecules that antagonise their action and which may be developed as clinical agents for patients with these malignancies.

Unfortunately, commercial realities probably mean that few companies will pursue treatments for these patients as

Table 2. Examples of cancer-associated chromosome translocations involving transcription factor (TF) genes

Disease	Translocation	Gene 1	Gene 2
APL	t(15; 17) (q21; q11–22)	*PML*	*RARα*
Pre B-cell ALL	t(1; 19)(q23; p13)	Homeodomain TF, *PBX1*	bHLH TF, *E2A*
Pro B-cell ALL	t(17; 19) (q22; p13)	bZIP TF, *HLF*	*E2A*
CML	t(3; 21) (q26; q22)	Zn-finger TF, *EVI-1*	New TF, *AML-1*
Ewing's sarcoma	t(11; 22) (q24; q12)	Ets TF, *FLI-1*	*EWS**
Malignant melanoma of soft parts	t(12; 22) (q13; q12)	bZIP TF, *ATF-1*	*EWS*
Rhabdomyosarcoma	t(2; 13) (q35; q14)	Homeodomain TF, *PAX3*	Forkhead TF, *FKHR*
Myxoid liposarcoma	t(12; 16) (q13; p11)	bZIP TF, *CHOP*	*TLS/FUS**

* The normal *EWS* gene encodes an RNA binding protein which contains a domain rich in glutamine, serine and tyrosine residues reminiscent of some TF activation domains. The *TLS* or *FUS* gene is homologous to *EWS* and both act as transcriptional activation domains in the fusion proteins resulting from the translocations involving their genes [35]. APL, acute promyeloptic leukaemia; ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia.

there are simply not that many cases. At the opposite end of the scale, are the 50% of human tumours thought to contain mutations in the tumour suppressor gene, *TP53*. The p53 protein is also an upstream transcription factor and it plays a pivotal role in the cell by monitoring the genome for damage and thence activating expression of a number of genes leading to either DNA repair or cell death (apoptosis), depending on the extent of the damage. Consequently, when *TP53* is mutated or deleted, a damaged cell has a greater chance of continuing to proliferate and ultimately forming a tumour. Biochemically, p53 has three major domains: an N-terminal transcription activation domain, a central sequence-specific DNA binding domain and a C-terminal domain which interacts with the central domain to autoregulate DNA binding. The majority of *TP53* mutations found in human tumours map to the central DNA binding domain, and recent work indicates that up to a third of these may result in too tight an interaction with the C-terminal autoregulatory domain leading to a failure to activate p53. Intriguingly, small peptides derived from the C-terminal domain can disrupt its association with the DNA binding domain, presumably by straightforward molecular competition, and hence activate p53. It is therefore, possible that small molecules in the form of peptides may be used to treat a large proportion of malignancies in order to rescue their p53 pathway, resulting in growth arrest and apopotosis within the tumour cells [36].

In more general terms, there are clearly a number of cellular genes whose expression is upregulated during tumorigenesis, and, if the encoded proteins are known to play a role in the maintenance, progression or failure of therapy of the tumour, then it may be of therapeutic benefit to try to antagonise this increased expression. Examples of such overexpressed genes include the extracellular proteases (e.g. cathepsin D, stromelysin-3, collagenases) which are believed to contribute to the metastatic potential of a tumour. Another good example is the multidrug resistance gene, *MDR1*, which encodes a membrane pump capable of removing from the cell a wide range of toxic compounds used as chemotherapy agents. In order to identify suitable transcriptional targets for these genes, it would first be necessary to understand something of the mechanism behind the control of their expression in the tumour cells. For example, our own work has concentrated on the control of transcription of the c-*erb*B-2 proto-oncogene in breast tumours. This receptor tyrosine kinase is overexpressed in 25–30% of breast and other solid tumours, and is associated with poor prognosis and a reduced response to conventional therapy. Consequently, a number of groups are looking at ways to inhibit the activity of this protein in order to improve prognosis in this patient group [37]. We have taken the approach of trying to determine how c-*erb*B-2 becomes overexpressed in tumours. Allthough the gene is frequently amplified, this does not fully account for the expression profiles observed and we have now shown that tumour cells which overexpress c-*erb*B-2 have acquired an additional upstream factor, which we have identified as the developmentally regulated transcription factor, AP-2 [38, 39]. We have also demonstrated that a small molecule which interferes with the DNA binding activity of AP-2 can downregulate c-*erb*B-2 expression *in vivo* [40]. Other groups have tried alternative approaches to antagonise c-*erb*B-2 transcription, for example, by using specific triplex helix oligonucleotides to inhibit transcription factor binding to the promoter [25, 41]. Although in themselves rather modest steps forward, these examples provide a paradigm for a novel approach to cancer therapy whereby transcriptional antagonists may be used, probably in combination with existing chemotherapy regimens, to improve the specificity of antitumour therapy in the future.

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