The Thioredoxin-Thioredoxin Reductase System: Over-Expression in Human Cancer

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Abstract. Redox control has emerged as a fundamental biological control mechanism. One of the major redox control systems is the thioredoxin system comprised of thioredoxin (TRX) and thioredoxin reductase (TR). Together they form a powerful system involved in many central intracellular and extracellular processes including cell proliferation, the redox regulation of gene expression and signal transduction, protection against oxidative stress, anti-apoptotic functions, growth factor and co-cytokine effects, and regulation of the redox state of the extracellular environment. Over recent years this system has increasingly been linked to the development and expression of cancer phenotypes. In this report immunocytochemical approaches have been used to simultaneously determine the expression and localisation of both TRX and TR in primary human cancers, including breast cancer, thyroid, prostate and colorectal carcinoma, and malignant melanoma. In aggressive invasive mammary carcinomas and advanced malignant melanomas, thioredoxin was highly over-expressed compared to tumours of lesser aggressive nature. TRX expression was found in both nuclear and cytoplasmic location in the neoplastic cells. Furthermore, increased levels of TRX positively correlate with thioredoxin reductase (TR) expression and localisation. These results, which are the first immunocytochemical studies of the in vivo expression and localisation of TRX and TR in carcinomas, thyroid, prostate and colorectal carcinomas and the first reports of TR expression in breast carcinomas, significantly extend the range of human cancers for which such data is available. Overall the results support the conclusion that aggressive tumours greatly over-express both TRX and TR. Such tumours have a high proliferation capacity, a low apoptosis rate and an elevated metastatic potential strongly implicating the involvement of the TRX system in the processes of oncogenesis and tumourigenesis and confirming its potential as a target for anti-cancer therapy for a wide range of human tumours.

The thioredoxin system is a major redox control system in mammalian cells and tissues which has been increasingly implicated in the development and expression of the cancer phenotype of several human cancers. Thioredoxins (TRXs) are small (12 kDa) redox active proteins with highly conserved active sites of -Cys-P-Cys- which participate in redox reactions through the reversible oxidation of this active site dihio1 (1). The oxidised thioredoxin is reduced by an NAPDH-dependent thioredoxin reductase (TR) and the reduced thioredoxin is a very effective protein disulphide reductase. Through this action it is able to effect the disulphide-dependent structural changes in other molecules, causing the activation or inhibition of target proteins (1). Thioredoxin reductases are the only enzymes known to be able to reduce the active site of TRX (2). Mammalian thioredoxin reductases are homodimeric, flavin adenine dinucleotide-containing proteins with a C-terminal seryl-cysteine residue (3, 4) that is essential for the activity of the mammalian thioredoxin reductases (5). In addition to catalysing TRX reduction, mammalian TRs are notable in having a wide substrate specificity encompassing many low molecular weight disulphide compounds and non-disulphide compounds such as lipids, hydroperoxides, dehydroascorbate and lipoprotein (6).

Together TRX and TR constitute the TRX system, a key cellular redox control system. Multiple protein substrates have been identified for thioredoxin, including ribonucleotide reductase (1) and various transcription factors (7) and so TRX is an essential part of the cell proliferation machinery and a key component in the redox regulation of gene expression. TRX is also involved in the redox regulation of apoptosis. Reduced TRX (but not oxidised TRX) inhibits apoptosis by an inhibitory binding to ASK-1 (8). Furthermore...
TRX possesses reactive oxygen reducing activity and so acts as a scavenger for reactive oxygen species (ROS) (9). TRX is also the electron donor to thioredoxin peroxidases (peroxiredoxins) important in the reduction peroxides and protecting cells from oxidative stress (9). Thioredoxin also has extracellular functions. TRX can be secreted by cells by a non classical pathway and can act as an autocrine growth factor as well as displaying co-cytokine activity augmenting the effects of other cytokines (10). Extracellular TRX may be bound to the external cell membrane where it may participate in and regulate cell to cell contact and contribute to redox regulation in the extracellular space (11).

TRX and TR are over-expressed in several tumour cells and both are secreted (12, 13) and recent work indicates the TRX system may have important roles to play in tumour development and malignancy. TRX and TR have been reported to be expressed at a high level in a number of cancers and transformed cell lines. For example, TRX mRNA is present in 3- to 100-fold elevated levels in almost half of the human primary lung and colon tumours examined, compared to adjacent normal tissues from the same patients (14). A number of human transformed cell lines have also been analysed and found to have 10-fold higher levels of TRX mRNA and 23-fold higher levels of TR mRNA (14). Thioredoxin stimulates the proliferation of both normal fibroblasts and a variety of human solid and leukemic cancer cell lines (15). It is secreted by these cells and so may act as an autocrine growth factor. Redox activity is essential for these growth stimulatory effects of TRX since redox-inactive mutant forms lacking the active site cysteine residues are devoid of these functions (15). Transfection of cells with TRX constructs increases cellular TRX expression and the density to which NIH3T3 cells will grow in culture and stimulates many fold the anchorage-independent colony formation by MCF-7 breast cancer cells (16). Transfection of WEHI 7.2 mouse thymoma-derived cells with TRX constructs stimulates tumour growth and inhibits apoptosis in vivo (17). Transfection of breast cancer cells with the gene encoding a redox inactive TRX mutant reversed the transformed phenotype of the cancer cells with the expressed protein acting as a dominant negative. Tumour formation by the redox mutant transfected MCF-7 cells on inoculation into scler mice was almost completely suppressed with only microscopic tumour cell deposits being observed and there was no evidence of metastasis to other organs (16).

While such studies implicate the TR system in the process of tumour development, there has been relatively few studies on the expression and localisation of TRX and TR in solid tumours. There have been reports of TRX expression and localisation in breast (18, 19), lung (20), gastric (21), pancreatic (22), hepatocellular (23) and cervical carcinomas (24) as well as in some leukemias (25). There have however been only two reports of the expression and localisation of TR in tumours namely in small cell carcinoma (26) and mesothelioma (27), and these are the only two studies in which the expression of both TRX and TR in the same samples has been investigated. In this report we extend these studies by examining for the expression and cellular localisation of both TRX and TR in a range of human tumours including breast, thyroid, prostate, colorectal and also melanoma. The results show that aggressive tumours greatly over-express TRX and TR. The relevance of these observations to the high proliferation rate, low apoptosis rate and elevated metastatic potential of the tumours is discussed in terms of the involvement of the TRX system in the processes of oncogenesis and tumourogenesis and the potential of the TRX system as a target in anti-cancer therapies.

**Materials and Methods**

**Tumour and normal tissues.** Tumours were obtained from the Kauai Cancer Centre. The following tumours were investigated: (1) mammary neoplasms (n=49), consisting of infiltrating ductal carcinoma (n=10), ductal carcinoma (n=10), lobular carcinoma (n=10), signet ring carcinomas (n=2), mucin producing adenocarcinoma (n=2), fibrosarcoma disease (n=5); the tumours are lymph node-negative and have a high nuclear proliferative index; (2) malignant melanomas (n=26), consisting of superficial spreading melanoma (n=10), melanoma

![Figure 1](image1.png)

**Figure 1. Thioredoxin (TRX) over-expression in a signet ring carcinoma of the mammary gland. Lymph nodes are tumour-negative. Heterogenous cytoplasmic and membrane thioredoxin immunoreactivity (red) is over-expressed in all tumour cores investigated. Magnification x 400.**

![Figure 2](image2.png)

**Figure 2. Infiltrating mammary gland ductal carcinoma showing nuclear expression of thioredoxin (red immunoreactivity) in the majority of tumour cells with some nuclei negative. Magnification x 1000.**

![Figure 3](image3.png)

**Figure 3. Thioredoxin (TRX) over-expression in a grade 5b mammary gland ductal carcinoma. Lymph nodes are all tumour-positive. Thioredoxin immunoreactivity (red) is over expressed in 74% of all tumour cores investigated. Magnification x 400.**

![Figure 4](image4.png)

**Figure 4. Thioredoxin (TRX) over-expression in a grade 4b mammary gland ductal carcinoma. Lymph nodes are all tumour-positive. Note intense cytoplasmic thioredoxin immunoreactivity (red). Magnification x 1000.**

![Figure 5](image5.png)

**Figure 5. Nuclear and cytoplasmic thioredoxin reductase (TRX-R) immunoreactivity (red) in a infiltrating ductal mammary gland carcinoma of a 60-year-old patient. Thioredoxin is over-expressed in 80% of all infiltrating ductal carcinomas investigated. Magnification x 400.**

![Figure 6](image6.png)

**Figure 6. Thioredoxin reductase (TRX-R) immunoreactivity in a infiltrating ductal mammary gland carcinoma. Magnification x 1000.**
Table 1. Thioredoxin (TRX) and thioredoxin-reductase (TRX-R) overexpression in human mammary carcinomas, malignant melanomas, thyroid neoplasms, prostatic neoplasms and colorectal carcinomas.

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Number of Subjects</th>
<th>% Over-expressed TRX</th>
<th>% Over-expressed TRX-R *</th>
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<tr>
<td>Mammary carcinoma</td>
<td></td>
<td></td>
<td></td>
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<td>Lobular</td>
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<td>30.0</td>
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<tr>
<td>Ductal</td>
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<td>60.0</td>
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<tr>
<td>Intraductal</td>
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<td>60.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Signet ring</td>
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<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Infiltrating ductal</td>
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<td>80.0</td>
<td>80.0</td>
</tr>
<tr>
<td>Mucin producing</td>
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<td>100.0</td>
<td>100.0</td>
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<tr>
<td>Phaeocytotic</td>
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<tr>
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<td></td>
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<tr>
<td>Superficial spreading</td>
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<tr>
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<td>80.0</td>
<td>70.0</td>
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<tr>
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<td>70.0</td>
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<tr>
<td>Invasive follicular carcin.</td>
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<td>50.0</td>
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<tr>
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<td>10</td>
<td>40.0</td>
<td>40.0</td>
</tr>
</tbody>
</table>

*Compared to corresponding normal tissue from the same subject.

(n=10), metastatic melanoma (n=6); (3) thyroid neoplasms (n=30), consisting of papillary carcinoma (n=10), papillary oncocytic neoplasm (n=2), invasive follicular carcinoma (n=8), follicular carcinoma (n=10); (4) prostate neoplasms (n=20), consisting of benign hyperplasia neoplasm (n=10), carcinoma (n=10); (5) colorectal carcinomas (n=10). Tissue was fixed in phosphate-buffered 4% paraformaldehyde (pH 7.4) overnight at 4°C, washed in several changes of Tris buffer at pH 7.4, routine processed and embedded in paraffin wax. Sections were cut at 5 μm thickness and mounted on 2% amineprophosphotin (APS)-coated microscope slides. Sections of 5 μm formalin-fixed, paraffin-wax-embedded tissues, obtained from locations adjacent to the tumours, were used as normal control tissue.

TRX and TR antibodies. Immunohistochemical localisation of TRX in tissue sections was performed using purified mouse anti-human TRX monoclonal antibody which has previously been characterised and used for TRX localisation in human (28) and marmoset (29) tissues. Immunohistochemical expression of TR was demonstrated using an anti-human TR antiserum prepared by immunisation of rabbits against purified human placental TR. The antiserum was assessed for specificity by Western Blot analysis against purified human TR and human cell and tissue extracts and detected a single 56kDa band of human TR.

Immunohistochemistry. Paraffin-embedded tissue sections were cut at 5 μm thickness and mounted on 2% amineprophosphotin (APS)-coated microscope slides. Sections were deparaffinised with xylene and brought to distilled water via descending series of alcohol. Endogenous peroxidase was blocked by application of 3% hydrogen peroxide in Tris buffer for 5 minutes at room temperature. Sections were rinsed in Tris buffer and placed in blocking solution of 20% normal goat serum in Tris buffer for 20 minutes at room temperature. Excess serum was lapped off and sections were incubated with diluted 1:100 purified mouse anti-human TRX monoclonal or rabbit anti-human TR antiserum, in a humidified chamber overnight at 4°C. Sections were then rinsed in Tris buffer and incubated with biotinylated goat anti-mouse or anti-rabbit gammaglobulin secondary antibody (Dako, Gistrup, Denmark), diluted 1:200, for 1 hour at room temperature. Sections were then rinsed in Tris buffer and incubated in avidin biotinylated peroxidase link complex (Dako) solution for 1 hour at room temperature. Following washing in three changes of Tris buffer, visualisation of the peroxidase was by application of 3-acetyl 9-ethylcarbazole (AEC) as chromogen (Dako) and 0.09% hydrogen peroxide in Tris buffer. The sections were rinsed in Tris buffer, nuclei counterstained in Mayer's haematoxylin and finally dehydrated in ascending series of alcohols, cleared in three changes of xylene and mounted with DePex. Controls for thioredoxin and thioredoxin reductase specificity were performed by omission of the anti-human TRX monoclonal antibody and anti-human TR rabbit antiserum, respectively.

Results

Thioredoxin. The results of these immunocytochemical analyses, using anti-human TRX and TR antibodies (Table 1), show that TRX and TR are both over-expressed in the cytoplasm and nuclei in the majority of mammary carcinomas (Figures 1-6), melanomas (Figures 7-9), thyroid carcinomas (Figure 10), prostate and colorectal carcinomas, compared to their normal tissue counterparts. In the case of the mammary carcinomas investigated, TRX over-expression was found in 40% of the lobular carcinomas, 100% of the signet ring carcinomas (Figure 1), 80% of the infiltrating ductal carcinomas (Figure 2), 70% of the ductal carcinomas (Figures 3, 4), 60% of the intraductal carcinomas and 100% of the

![Figure 1](#) Thioredoxin (TRX) over-expression in a superficial-spread melanoma of Clark III level. Thioredoxin is over-expressed in 40% of all superficial melanomas investigated. Majority of lymph nodes are immunonegative. Magnification x 400.

![Figure 2](#) Thioredoxin (TRX) immunoreactivity (red) in a nodular melanoma of Clark level IV. Thioredoxin is over-expressed in 80% of all nodular melanomas investigated. Majority of lymph nodes are immunopositive. Magnification x 400.

![Figure 3](#) Membrane cytoplasmic thioredoxin-positive (TRX-R) immunoreactivity (red) in a nodular melanoma of Clark level IV. TRX-R is over-expressed in 70% of all nodular melanomas investigated. Magnification x 1000.

![Figure 4](#) Thioredoxin reductase (TRX-R) over-expression in an invasive follicular carcinoma of the thyroid gland. Note intense cytoplasmic and some nuclear immunoreactivity (red). TRX-R is over-expressed in 70% of all invasive follicular thyroid carcinomas investigated. Magnification x 1000.
mucin-producing carcinomas (Table 1). In contrast, only 20% of the fibrocystic diseases investigated showed TRX over-expression (Table 1). In the case of the malignant melanomas investigated, TRX was over-expressed in 40% superficial spreading malignant melanomas (Figure 7), 80% of the nodular malignant melanomas (Figure 8) and 40% of the metastatic melanomas were over-expressed (Table 1). Of the prostate neoplasms investigated, 10% of the benign prostatic hyperplasia diseases and 30% of the prostate cancers were TRX over-expressed (Table 1). In the case of the colorectal carcinomas investigated, TRX was over-expressed in 40% of the cases (Table 1). In the case of the thyroid carcinomas investigated, TRX over-expression was found in 70% of the papillary carcinomas, 50% of the oncocytic papillary carcinomas, 60% of the follicular carcinomas and 70% of the invasive follicular carcinomas (Table 1).

**Thioredoxin reductase.** TR, the enzyme involved in the reduction of TRX, was also present in large amounts in the cancer tissues, probably reflecting that a large amount of its substrate (TRX) is also present. In the case of the mammary carcinomas investigated, over-expression of TR was found in 30% of the lobular carcinomas, 60% of the ductal carcinomas, 60% of the intraductal carcinomas (Figures 5, 6), 100% of the signet ring carcinomas, 80% of the infiltrating ductal carcinomas (Figure 6) and 100% of the mucin-producing carcinomas (Table 1). In the case of the malignant melanomas investigated, 30% of the superficial spreading melanomas, 70% of the nodular melanomas (Figure 9) and 30% of the metastatic melanomas were TR over-expressed (Table 1). In the case of the thyroid carcinomas investigated, over-expression was found in 70% of the papillary carcinomas, 50% oncocytic papillary carcinomas, 70% of the follicular carcinomas and 80% of the invasive follicular carcinomas (Figure 10, Table 1). Of the prostate neoplasms investigated, 30% of the carcinomas were TR over-expressed, while no increase was observed in the benign prostatic hyperplasia diseases (Table 1). In the case of the colorectal carcinomas investigated, TR was over-expressed in 40% of the cases investigated (Table 1).

**Discussion**

The results reported here are the first immunocytochemical studies on the in vivo expression of TRX and TR in melanomas, thyroid, prostate and colorectal carcinomas and the first reports of TR expression in breast carcinomas. TRX and TR were found in both nuclear and cytoplasmic locations in the neoplastic cells. Furthermore, increased levels of TR positively correlated with TRX expression in all tumours examined. There have been two previous reports of TRX over-expression in breast carcinoma (18, 19). Also Bini et al. (30) by determining protein expression profiles detected the consistent high expression of TRX in breast ductal carcinoma compared to normal tissue. The present results confirm and extend these observations by also demonstrating the over-expression of TR. Furthermore, the association of TRX and TR staining with advanced tumour grades suggests a positive association of enhanced expression of these two proteins with the more aggressive phenotypes.

To our knowledge, there have been no previous reports of TRX or TR expression in melanomas in vivo. However Barral et al. (31) have reported that TRX and TR are highly expressed in cultured normal skin melanocytes and malignant melanoma cell lines. With prostate cancer Suzuki et al. (32) have noted elevated expression of TRX in hormone-independent prostate cell lines derived from bone metastases and suggest that this and elevated levels of other antioxidant systems observed may contribute to the resistance of metastatic prostate cancer to chemotherapy. The present immunocytochemical results on the expression of TRX and TR in colorectal carcinomas are also in keeping with previous observations. Berggren et al. (14) reported that TRX mRNA levels were increased 2- to 100-fold in 50% of human primary colorectal carcinomas compared to adjacent normal colonic mucosa from the same subject. Also, in the same carcinomas, TR activity and protein levels were increased at least 2-fold compared to normal mucosa.

From our present studies and the previous reports of TRX expression of tumours in vivo and by tumour cell lines in vitro, a general picture emerges of increased TRX/TR expression associated with tumourigenesis. While there are no doubt very significant differences between individual cancer types, the overall results suggest that over-expression of the TRX system contributes significantly to various aspects of the different cancer phenotypes. Indeed there is significant evidence which correlates the expression of these proteins with the proliferative capacity, apoptotic resistance and metastatic potential of different cancers.

In addition to its roles in cell proliferation and control of gene expression, secreted TRX can also act as an extracellular growth factor for both normal and tumour cells and can enhance the sensitivity of the cells to other growth factors (19). Breast cancer cells transfected with TRX show increased anchorage-independent growth while a redox inactive TRX mutant acts in a dominant negative fashion to inhibit proliferation and also tumour formation in nude mice (16). Consistent with this, Groen et al. (21) have observed in vivo a positive correlation between TRX over-expression and cancer cell proliferation in primary gastric carcinomas. In addition to its proliferative effects, TRX is also known to express anti-apoptotic effects, TRX inhibits apoptotic signalling by scavenging ROS and also by inhibiting the activity of ASK-1 (8). In studies of TRX expression in gastric
cell carcinoma Groen et al. (31) also noted a significant negative correlation between TRX over-expression and apoptosis suggesting a role for TRX in decreased apoptosis and increased carcinoma cell survival. In a study of non-small cell lung carcinomas Soini et al. (26) also observed that apoptosis was inversely associated with TRX and TR expression, again indicating that an anti-apoptotic effect of the TRX system may contribute to tumour cell survival.

Both TRX and TR are known to be secreted by cells including normal and cancer cells. Indeed elevated TRX levels have been observed in the plasma of patients with hepatocarcinomas (33) and pancreatic cancer (22). Recently it has been shown that secreted TRX can regulate the redox state of specific cell surface receptors (34) and of the extracellular environment (35). Consequently TRX may exert a redox control over cellular mechanisms that are involved with cell attachment, invasion and metastasis. In keeping with this Farina et al. (36) have also provided direct evidence that the extracellular TRX system contributes to the invasive capacity of SK-N-SH neuroblastoma cells in vitro and this is due in part to redox regulation of the functional MMP/TIMP balance governing MMP activity expression. In this pivotal study Farina et al. (36) demonstrated that TRX stimulated the invasive capacity of SK-N-SH neuroblastoma cells in a Matrigel invasion assay and that the TR inhibitor aurothioglucone inhibited the capacity of TRX to stimulate invasion, indicating that the redox activity of the TRX system was required for this function. Moreover it was shown that TRX inhibited the activities of both TIMP-1 and TIMP-2. It also inhibited MMP-2 at higher doses but it did not inhibit MMP-9. It was further shown that TRX not only stimulated basal neuroblastoma cell invasion but also reversed the capacity of exogenous TIMP-1 to inhibit both basal and MMP-9 stimulated invasion. In the present studies we noted in aggressive invasive breast carcinomas and advanced melanomas for example, TRX and TR were over-expressed compared to tumours of a less aggressive nature. Similar observations have been made for a number of other tumours in vivo for example Kakoyiannis et al. (20) noted that the over-expression of TRX in small cell carcinomas was correlated with the more aggressive phenotype and was associated with poor prognostic features. Similarly Nakamura et al. (32) have reported on a possible association of TRX over-expression with the malignant potential with pancreatic ductal carcinoma.

Given the association of the over-expression of the thioredoxin system with the processes of tumourigenesis and malignancy reported here and elsewhere, the targeted inhibition of the TRX system has been suggested as a novel approach for the treatment of some cancers. Indeed specific chemical inhibitors of TRX and TR are known to inhibit cancer cell growth and exhibit anti-tumour activity in vivo. For example, some alkyl 2-imidazolyl disulfide inhibitors of TRX have been shown to have anti-tumour activity against human tumour xenografts growing in nude mice (37). Also Kunkel et al. (38) utilised an algorithm to search the NCI investigational drug database of known cytotoxic agents for similar compounds to known TRX/TR inhibitors. Of the 40 compounds identified, 37 exhibited anti-TR activity. 3 were TRX inhibitors and several were already known to be potent anti-tumour drugs. Moreover other studies indicate that other potential therapeutics may achieve their anti-tumour effects through down-regulation of the TRX system. The recent work of Butler et al. (39) demonstrates that such down-regulation accounts at least in part for the action of histone deacetylase inhibitors such as SAHA which induce growth arrest, differentiation and/or apoptosis of transformed cells in vivo and inhibit tumour growth in vivo. SAHA induces the expression of thioredoxin-binding protein-2 (TBP-2), also known as vitamin D upregulated protein (VDUP), which binds to and inhibits TRX activity and also results in a decreased expression of TRX. TRX/FR over-expression has also associated with the development of drug resistance in several tumour cells and cell lines. For example Yekizou et al. (40) demonstrated that increased levels of TRX in prostatic and bladder cancer cell lines are associated with drug sensitivity to cisplatin, mitomycin C, doxorubicin and etoposide. Further studies show that inhibition/down-regulation of TRX/TR expression sensitises drug-resistant tumour cells to drug action, clearly establishing the link between the TRX system and drug sensitivity (41, 42). Clearly drugs that target the TRX system either directly or indirectly have potential as therapeutic drugs, either singularly or in combination with other therapeutic agents.

In conclusion, these studies have demonstrated the over-expression of the TRX system in a range of human tumours including breast, thyroid, prostate and colorectal carcinomas as well as melanomas and an association with the more aggressive tumour phenotypes. Such tumours have a high proliferation rate, a low apoptosis rate and an elevated metastatic potential, all of which can be influenced by the actions of the TRX system. As such these studies further emphasise the potential of anti-TRX system agents as anti-cancer therapeutics in the treatment of a wide range of human tumours.

References


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