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PERSPECTIVES

The potential role of thioredoxin 1 and CD30 systems as multiple pathway targets and biomarkers in tumor therapy

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Abstract Our progress in understanding pathological disease mechanisms has led to the identification of biomarkers that have had a considerable impact on clinical practice. It is hoped that the move from generalized to stratified approaches, with the grouping of patients into clinical/therapeutic subgroups according to specific biomarkers, will lead to increasingly more effective clinical treatments in the near future. This success depends on the identification of biomarkers that reflect disease evolution and can be used to predict disease state and therapy response, or represent themselves a target for treatment. Biomarkers can be identified by studying relationships between serum, tissue, or tumor microenvironment parameters and clinical or therapeutic parameters at onset and during the progression of the disease, using systems biology. Given that multiple pathways, such as those responsible for redox and immune regulation, are deregulated or altered in tumors, the future of tumor therapy could lie in the simultaneous targeting of these pathways using extracellular and intracellular targets and biomarkers. With this aim in mind, we evaluated the role of thioredoxin 1, a key redox regulator, and CD30, a cell membrane receptor, in immune regulation. Our results lead us to suggest that the combined use of these biomarkers provides more detailed information concerning the multiple pathways affected in disease and hence the possibility of more effective treatment.

Keywords Biomarkers · Immunotherapy · CD30 · Thioredoxin · Cytokines · Dual target

Introduction

The identification of biomarkers has had a considerable impact on clinical practice [1]. As a general rule, if tumor biomarkers are to be of practical use they must either reflect a particular characteristic or stage of disease or represent a target for therapy. One of the best ways to diagnose cancer early, aid in its prognosis, or predict therapeutic response, is to use serum, tissue, or tumor microenvironment biomarkers. Prognostic biomarkers are used to predict the course of the disease, including recurrence and therefore have an important influence on the choice of therapy [2]. Stratification (predictive) biomarkers predict the response to a drug before treatment starts by classifying individuals as likely responders or non-responders. These biomarkers are usually identified from system biology-type studies that look at biological factors that influence not only the pathogenesis but also the progression of the disease. Given that multiple pathways are deregulated or altered in tumors, for example those responsible for redox and immune regulation, it is more than probable that future tumor therapy will involve simultaneous targeting of pathways, through the use of extracellular and intracellular prognostic and stratification biomarkers.

Redox system pathways regulate multiple cellular processes including proliferation, cellular cycle, death, and

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survival pathways [3–5] and influence the phenotypic, functional, and apoptotic homeostasis of both immunological and tumoral cells. In these pathways, the cell thiol redox state is a crucial mediator of multiple metabolic signaling and transcriptional processes. In a metabolically active cell, these redox system pathways maintain the balance between oxidant and antioxidant factors, by regulating the activation of specific transcription factors and the production of substances that neutralize oxidants [5, 6]. However, when as in tumor, there are alterations in the pathways of the redox system, the cell is no longer able to produce antioxidant substances and adjust the balance between oxidant and antioxidant factors, and therefore, it is unable to respond appropriately to the body's needs. This is usually the reason why many anticancer agents including radiation are ineffective, because the cytotoxicity induced by them to make the cancer regress affects the antioxidant activity of the redox system pathways, which are altered for the reasons explained above [7]. Alterations in the physiological pathways involved in the regulation of the redox system have been identified in tumors [3–6, 8], and research indicates that the functional inactivation of immune cells by free radicals is an important immunosuppressive mechanism [8]. The re-establishment of homeostasis within the physiological pathways of the redox and immunological system is thus an important therapeutic goal in tumor treatment, and biomarkers and targets are essential for this.

Thioredoxin 1 (Trx1), a thiol-disulfide oxidoreductase, is an essential physiological redox regulator in cellular reactions [6]. As a result of oxidative stress, Trx1 activates specific transcription factors in the nucleus that regulate gene decoding for the production of substances that protect cells from oxidative stress induced by free oxygen radicals. Consequently, the fairly recent discovery that Trx1 catalytically interacts with a target protein, the CD30 cell membrane receptor (CD30R), on immune cells (T, B, monocytes, dendritic cells, NK, eosinophils and granulocytes), is of great clinical significance [9–11]. CD30, although not well known, is a molecule with a wide range of action including regulatory signaling responsible for the physiological homeostasis of T helper (Th)1/Th2/Th3/Th17 cell network functions and hence for a productive immune response [12–16]. The soluble (s) component of CD30 (sCD30) and Trx1 both regulate CD30R functional activation [9, 11], and abnormal increases in the levels of both result in Th1-cell functional deficit [12–14, 17, 18] and have been noted in cancer [19, 20].

In light of the above, we assessed the potential of the combined use of Trx and the CD30 system as a dual biomarker for extracellular and intracellular pathways and propose their simultaneous targeting in tumor redox/immunotherapy.

Trx1 system pathways and their importance in physiological regulation

The redox system is one of the most important regulatory systems of cell physiology in living organisms [6]. The Trx system, consisting of Trx, thioredoxin reductase (TrxR), and NADPH, is a key regulator in cellular redox reactions. The cells of mammals contain two main Trx/TrxR systems: the Trx1/Tx1R system that is normally found in the cytoplasm but under stress can migrate into the nucleus to induce gene transcription or be secreted into the extracellular environment to participate in the immune system network and the Trx2/Trx2R system that is located in mitochondria and endoplasmic reticulum and regulates cellular apoptosis. There is also a mammalian testis-specific thioredoxin system that consists of three thioredoxins that are only expressed in spermatids (named Sptrx-1, Sptrx-2, and Sptrx-3) and an additional thioredoxin, highly expressed in testis, but also present in lung and other ciliated tissues (named Txl-2) [21].

Trx1 consists of 108 amino acids; it contains a disulfide bridge, and its catalytic site (-Trp-Cys^{32}-Gly-Pro-Cys^{35}-Lys) uses hydrogen as a donor for oxidoreduction reactions. Its reduced form is able to reduce ribose or phosphate ribonucleosides, and the oxidized form is converted into the reduced form by the flavoprotein Tx1R, with the intervention of NADPH, forming the "thioredoxin1 redox-system" (Fig. 1). The Trx1 system operates in cellular redox signaling by controlling the activity of transcription factors such as NF-kB, p53, HIFa, AP-1, and the glucocorticoid receptor [6, 18, 22, 23].

Human T cells transformed by viruses produce a factor, previously known as ADF, which is identical to human Trx1. Trx1 is secreted by activated B lymphocytes, B lymphocytes in chronic type-B leukemia, T lymphocytes, and fibroblasts. Trx1 is a potent growth factor and cell survival factor and its expression rises in several types of tumor especially more aggressive ones [24–29], and it is generally related to tumor aggressiveness and inhibition of the immune system [8]. Trx has been evaluated as a biomarker and therapeutic target for cancer [30–32], and it is known that Trx levels can be used to indicate potential chemotherapy resistance [8, 33, 34]. Indeed, an increase in the level of Trx1 has been associated with decreased survival in tumor patients, and it is used as an independent prognostic factor for progression and the expression of VEGF and Ref-1 [29].

Trx1 catalytically interacts (Fig. 1) with a target protein on immune cells, the tumor necrosis factor receptor superfamily member 8 (TNFRSF8/CD30R) [9]. The redox interaction is highly specific for both Trx1 and CD30R, and the consequent redox state of CD30R determines its ability to engage the cognate ligand CD30L and transduce signals

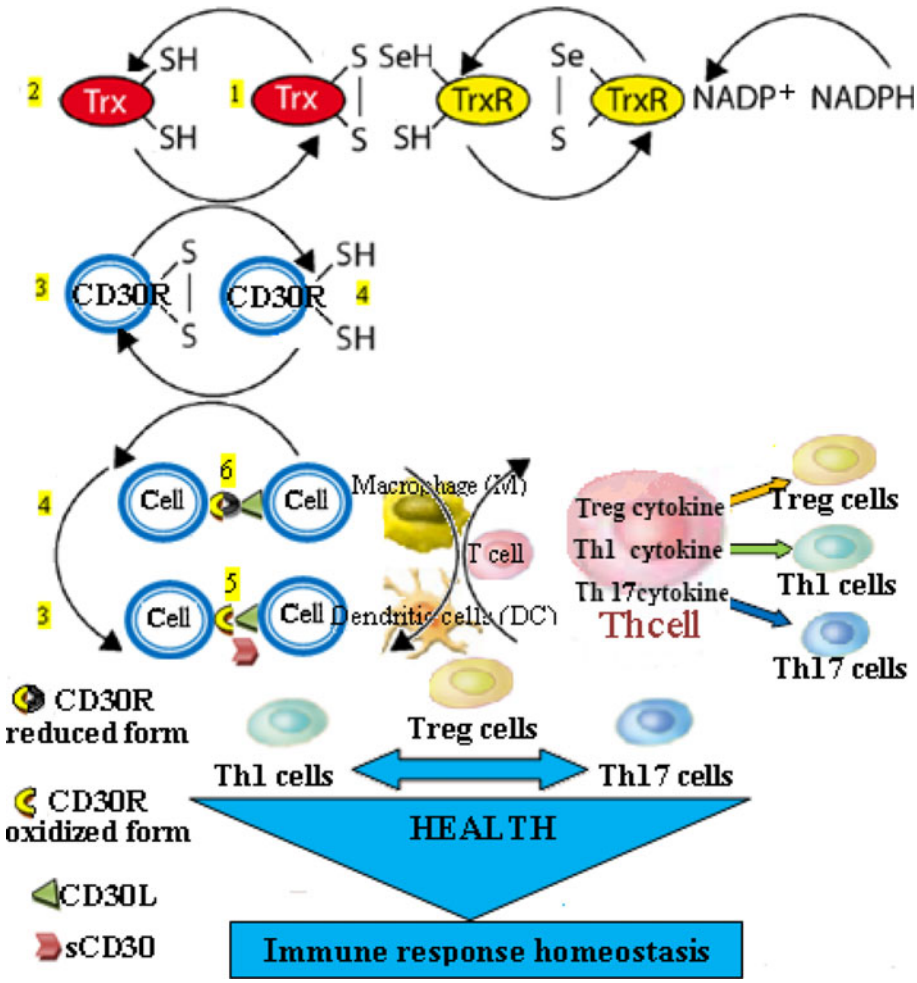

Fig. 1 Trx1 has a conserved catalytic site (-Trp-Cys-Gly-Pro-Cys-Lys) that undergoes reversible oxidation to the cysteine-disulfide (Trx-S2) form through the transfer of reducing equivalents to a disulfide substrate (X-S2). In health, the oxidized (*1*) Trx1 form (Trx-S2) is converted back to the cysteine-thiol reduced (*2*) form [Trx-(SH)2] by the NADPH-dependent flavoprotein thioredoxin reductase (TrxR), so maintaining balance between oxidized and reduced Trx1 forms, and catalytically interacts with CD30 cell membrane receptor (CD30R) on the immune cells (*9*). The consequent oxidized (*3*) and reduced (*4*) states of CD30R determine its respective ability (*5*) or inability (*6*) to engage its ligand CD30L. In this way, it is possible to transduce signals of M and DC intracellular pathways for Treg/Th1/Th17 cytokine production, leading to balance of Th differentiation into Treg/Th1/Th17 cells, for immune response homeostasis

[9]. Thus, Trx1 could be used as an extracellular biomarker to reflect CD30-dependent changes in lymphocyte effector function because extracellular Trx levels regulate the redox status of CD30R and binding of its ligand (CD30L) to CD30R (Fig. 1).

The CD30R, CD30L, sCD30, and their importance in immune system homeostasis

The CD30R, a member of the superfamily of TNFR/NGFR receptors, was originally identified on primary cultures of Hodgkin and Sternberg cells. CD30R is also expressed on normal activated T cells, B cells, NK cells, dendritic cells, and macrophages. Activation-induced expression implicates CD30R as one of the regulators of the ensuing immune response. The physiological function of CD30R is not yet clear, but there is evidence that it behaves as a signal transduction molecule. The interaction between CD30R and CD30L on activated T cells, monocytes, neutrophils, eosinophils, and B cells induces rapid activation of gene transcription factors such as JunN-kinase and NFKB. Furthermore, CD30R signals have been shown to induce and regulate the integrated expression of lymphocyte genes, cytotoxic effector molecules, nodal traffic, proliferation, and apoptosis [35]. Under inflammatory conditions, CD30R expression increases and its in vivo activation can be assessed and monitored by measuring the level of sCD30, shed from the plasma membrane upon CD30L binding to CD30R. CD30R was originally identified as a promoter of Th2-cell development and was used as a marker for Th2-cell populations [36, 37]. However, further studies have identified CD30R+ cells in Th0, Th1, and Th2 profiles and shown that during the course of a normal antigen response, CD30R+ cells are the main producers of IL5 and IFNγ [38]. The production of IFNγ by CD30R+ cells has been linked to a TH1 response, while the production of IL4 to a Th2 response. Current research indicates that CD30R and sCD30 levels are involved in the homeostatic regulation of the entire network of Th populations (Th1/Th2/Th3/Th17) [12, 16].

The Th1/Th2/Th3/Th17 cell network and its significance in physiological homeostasis

The immune response has classically been divided into two types: type 1 (Th1) the cell-mediated response, and type 2 (Th2) the humoral immune response. These responses are regulated by Th1 and Th2 subsets of CD4+ Th cells. Both subsets produce interleukin (IL) 3, granulocyte monocyte colony stimulator factor (GMCSF) and tumor necrosis factor (TNF) α, but only Th1 cells produce IL2 and IFNγ, while Th2 cells produce other cytokines such as IL4, IL5, IL6, and IL10. However, for a normal immune system function, the polarization of the immune response into Th1 or Th2 cell types should not be absolute and the ratio of these cells must vary according to physiological demand and clinical conditions [39, 40], and return to initial levels in physiological homeostasis. Each Th cytokine plays a specific and crucial role in maintaining the balance within the Th cell network, which is responsible for the normal development of the immune response.

An additional CD4+ Th-cell subset designated Th3 [41] was later identified, and it is functionally characterized by the production of transforming growth factor (TGF)β. These cells have a very important T-regulatory role (T-reg) on Th1- and Th2-cell functions, and increased effort is being made in pharmacological research to understand the mechanisms behind TGFβ-mediated Th1/Th2 immunological suppression and/or stimulation.

A further population of T cells (Th17 cells) producing IL17, IL6, TNF has also been identified, and it has been reported that TGFβ and IL6 interaction induces Th17-cell differentiation in autoimmunity progression, by switching T-cell generation from Treg to Th17 cells [42, 43]. On the basis of this new Treg/Th1/Th2/Th17 model, Treg and Th17 cells generate from reciprocal developmental pathways, and IL6 and TGFβ appear to be the chief inducers of Th-17 development while TGFβ alone promotes the generation of Treg cells. CD30 appears to regulate the differentiation of Th cells into Treg or Th17 cells [14], and both Th1 and Th2 cytokines are required to reduce IL17.

Consequently, Th1 cells, long thought to mediate tissue damage, might only be involved in the initiation of tissue damage, without playing a decisive role. The cytokine IL17, on the other hand, is now thought to have a major role in various immune-mediated injuries including tumor [44], organ-specific autoimmunity, allergic disorders of the lung and skin, and microbial infections of the intestine and nervous system.

In this new context, the immunological function of Th1-cell population would be to antagonize Th17 pathways to counter the onset of the above-mentioned diseases. Without a doubt, a greater understanding of Treg/Th1/Th17 pathways will lead to a shift in perspective concerning the functional basis of the immune system and lead to improvements in the prevention and treatment of tumor [44] and other immune pathologies. Clearly, given the interconnecting role of the Trx1 and CD30 systems in the regulation of Treg/Th1/Th17 pathways described earlier (Fig. 1), they offer great potential as targets and biomarkers for new pharmacological treatments.

CD30R/sCD30 and their regulatory role in the Treg/Th1/Th17 network

The use of the CD30 system as a biomarker and therapeutic target for cancer (19) has been investigated by various authors [19, 36, 37, 45]. The hypothesis that CD30 system is responsible for the homeostasis of the Treg/Th1/Th17 cell network was confirmed when it was found that CD30R-mediated signals trigger changes in the levels of production of several important Th cytokines involved in the regulation of Treg/Th1/Th17 cell network homeostasis [12–16, 35, 38, 44, 46]. These results also showed that when interaction between CD30R and CD30L was blocked by an abnormal increase in the levels of sCD30 [47], there was an imbalance between Treg/Th1/Th17 cell functions similar to the imbalance described for a monoclonal CD30R antagonist [12] or monoclonal antibodies blocking IL4 or IFNγ activity [12, 46]. The expression and function of the CD30R in dendritic cells (DCs) was also found to have a fundamental role in the production of Th cytokines and regulation of Treg/Th1/Th17 cell network homeostasis [13, 14, 48]; abnormal increases in sCD30 levels produced a disruption of DC CD30R-mediated signals by inducing alterations in the immature DC and DC regulation of Treg/Th1/Th17 cell immune response balance.

Thus, an abnormal increase in the levels of sCD30 can produce an imbalance between Th cell network functions (Fig. 2), by blocking CD30R-mediated signals [47]; sCD30 levels have also been found to be a prediction factor for immunological risks [14, 19, 36, 37]. A lack of Treg can also be a consequence of alterations in the normal regulation of Th cell network through CD30R [12–14]. It has become clear that DCs, through CD30R, play an essential role in inducing and modulating Treg [12–16, 48], and there is increasing evidence that targeted stimulation of Treg may promote health and significantly reduce the risk of cancer [42, 49].

Hence, in conclusion, it would appear that (i) CD30R-mediated signals are responsible for the homeostasis of important Th cytokines involved in the regulation of Treg/Th1/Th17 cell network homeostasis (Fig. 1 and Online Resource 1); (ii) altered CD30/CD30L interaction due to abnormal increases in sCD30 is responsible for a lack of this regulation and the consequence of this is disease [44]

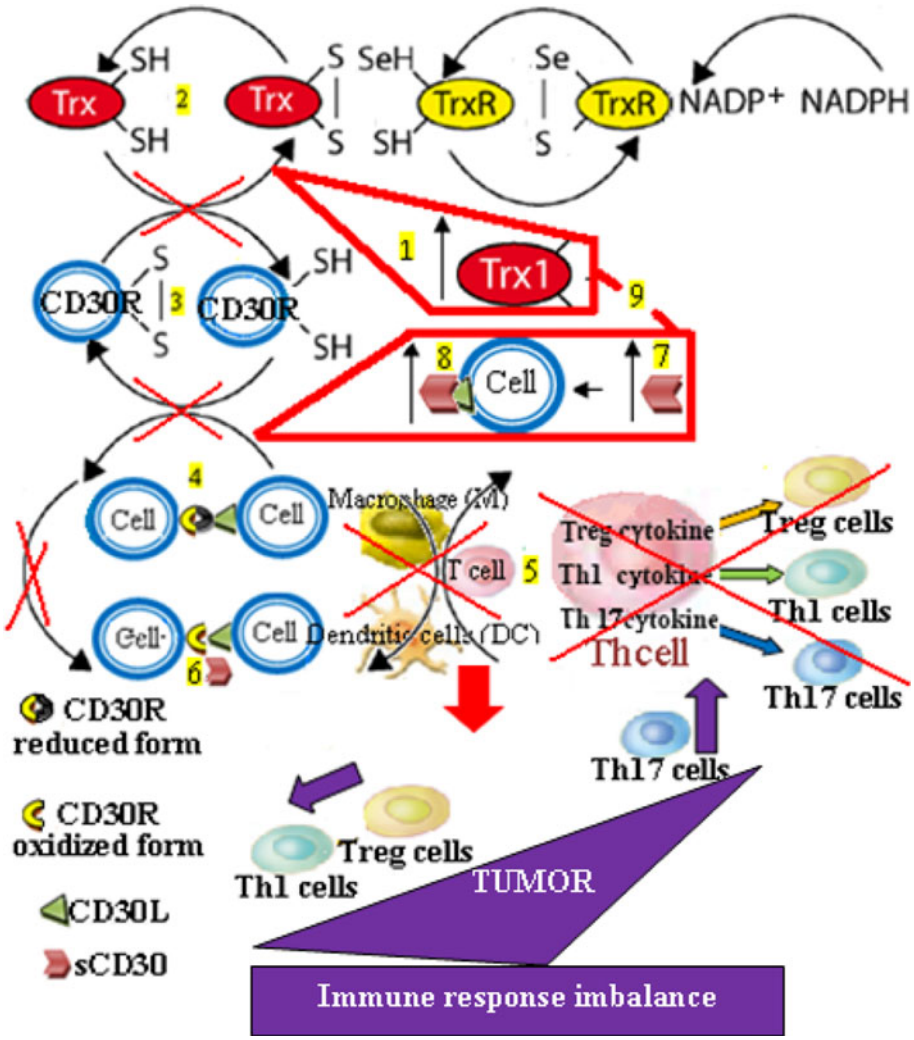

Fig. 2 In tumors, an increase in Trx1 levels (*1*) leads to abnormal redox cellular regulation determining imbalance between oxidant and antioxidant Trx1(*2*) and between oxidized and reduced states of RCD30 (*3*), so establishing RCD30 inability to engage CD30L (*4*) and transducer signals of intracellular pathways for Treg/Th1/Th17 cytokine production (*5*). When levels of sCD30 (shed from the plasma membrane upon CD30L binding (*6*) increase (*7*), sCD30 binds to CD30L with high affinity blocking CD30/CD30L transmembrane signaling (*8*). Thus, abnormal increases in the levels of Trx1 and sCD30 (biomarkers 9 of extracellular pathways of Trx1/CD30 target) result in both deregulation of M and DC pathways of Treg/Th1/Th17 cytokine production (biomarkers 5 of intracellular pathways of Trx1/CD30 target) and immunological deficit: Th17 expansion and Treg and Th1-cell functional deficit

(Fig. 2 and Online Resource 2); (iii) sCD30 can also be used as an extracellular biomarker reflecting CD30R-dependent changes in lymphocyte effector function (Fig. 3) because extracellular sCD30 levels regulate the ligand binding of CD30L to CD30R (Figs. 1, 3).

CD30 and the Trx1 system: their clinical, diagnostic, and therapeutic potential

The pathways mediated by RCD30 are therefore responsible for the homeostasis of the Th cell network, through the regulation of Treg/Th1/Th17 cytokine production by monocytes, immature and mature dendritic cells that direct the differentiation of Th cells (Fig. 1).

However, an abnormal increase in sCD30 levels prevents this regulation by close binding to CD30L, thus blocking its interaction with membrane-bound CD30R [47] (Fig. 2 and Online Resource 2). Hence, sCD30 could potentially have a clinical, diagnostic, and therapeutic role as an extracellular biomarker (Fig. 3) in immunopathologies such as tumors [10, 11].

Trx1, on the other hand, catalytically interacts (Fig. 1) with CD30R [9] determining its ability to engage the cognate ligand CD30L and transduce signals. Thus, Trx1 also affects CD30-dependent changes in lymphocyte effector function by regulating its redox status and ligand binding of CD30L. Increases in Trx1 levels (Fig. 2 and Online Resource 2) have been linked to a lack of this regulation: serum level values of Trx1 (Table 1), which in normal individuals range between 10 and 80 ng/ml (0.8–6.6 nM) [28], have been reported to be elevated in several human primary cancers (Table 1), including lung, colon, cervix, liver, pancreatic, colorectal, and squamous cell cancer [28, 50, 51] (Table 1) and are generally related to tumor aggressiveness [24–29] and inhibition of the immunological system. Serum levels of sCD30 (Table 1), which are usually below detectable levels or present at very

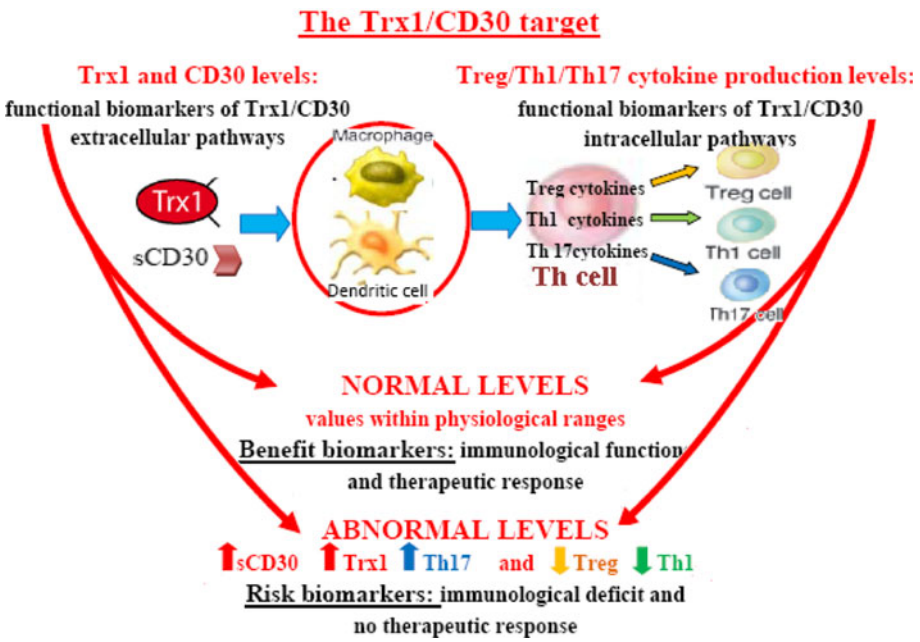

Fig. 3 Levels of Trx1/sCD30 and Treg/Th1/Th17 cytokine in serum, tissue, or tumor microenvironment are prognostic and stratification biomarkers for clinical treatment. The CD30/Trx1 system is a potential target in tumor therapy aimed at the simultaneous optimization of the redox and immune system regulation. Normal levels of sCD30 and Trx1 are positive (benefit) biomarkers reflecting the normal functioning of extracellular pathways, while normal levels of Treg/Th1/Th17 cytokines are positive (benefit) biomarkers for the normal functioning of intracellular pathways. Abnormal levels (higher levels of sCD30, Trx1, and Th17 and lower levels of Treg and Th1) are negative (risk) biomarkers for the abnormal functioning of CD30/Trx1 target pathways and so for immunological deficit and a lack of response to therapy

low levels between 0 and 10 pg/ml [19, 28], have also been reported to be elevated in several human primary cancers (Table 1), including colorectal, Hodgkin's lymphoma, prostate, lung and ovarian cancer, and are generally related to tumor aggressiveness [52, 53] and inhibition of the immunological system. Serum levels of sCD30 mirror Trx1 levels in physiological networks [9]: as Trx1 levels increase in infections, allergies, autoimmune events, and cancer, so do sCD30 levels; likewise Trx1 levels modulate CD30R immunological functions during the immune response as do sCD30 levels.

So in light of the facts that (i) RCD30 is highly expressed on immune cells in inflammatory situations and levels of sCD30 and Trx1 increase in the extracellular environment, (ii) changes in the level of sCD30 and Trx1 within normal ranges are linked to physiological immunological homeostasis (Fig. 1 and Online Resource 1), while significantly high levels of sCD30 are related to the prevalence of Th17 suppressive immunity and Treg/Th1 immunological deficiency (Fig. 2 and Online Resource 2), and (iii) higher levels of sCD30 and Trx1 have been found in pathological processes including cancer (Table 1), it can be concluded that (i) the Trx1/CD30 system could represent a new dual target and biomarker in tumor treatments (Fig. 3) and (ii) the levels of Trx1/sCD30 and Treg/Th1/Th17 cytokines could be used as prognostic and stratification biomarkers for extracellular and intracellular pathways in therapy aimed at the simultaneous optimization of the regulation of redox and immune system functions (Fig. 3).

Conclusions

The identification of prognostic and stratification biomarkers in clinical practice has resulted in the transition from a generalized approach to a stratified one, with treatment and diagnosis based on the identification of specific, subgroups of patients. However, this type of approach relies on the definition of real clinical targets and biomarkers which can be easily assessed, early in the disease process.

The potential of Trx and CD30 for use as targets and biomarkers for tumors has been widely described in literature, and alterations in the physiological pathways involved in the regulation of the redox and immunological systems have been identified in various types of tumors such as colorectal cancer, non-small cell lung carcinoma, and breast cancer. However, we believe that it would be more effective to target Trx and CD30 together to optimize the regulation of redox and immune system functions, as by combining these systems we combine the power of redox-sensitive factors with the specificity of immune system

Table 1 Physiological levels of Trx and sCD30 and levels defining them to be overexpressed and thus indicative, as biomarkers, of a cancer state

	Sample	Mean control	Mean disease	References
Trx1				
Hepatocellular carcinoma	Serum	80.9 ng/ml	125.5 ng/ml	Miyazaki [54]
Pancreatic carcinoma	Plasma	24.4 ng/ml	54.8 ng/ml	Nakamura [55]
Non-small cell lung cancer	Serum	30.1 ng/ml	195.9 ng/ml	Okamoto [56]
Colorectal, squamous cell, appendiceal pancreatic, renal, sarcoma, hepatocellular, gastroesophageal, non-small cell lung cancer, cholangiocarcinoma	Plasma	27.6 ng/ml	182.0 ng/ml	Baker [57]
sCD30				
Colorectal cancer	Serum	3.7 pg/ml	15 pg/ml	Del Beato [19]
Hodgkin's lymphoma	Serum	4.0 U/ml	65 U/ml	Visco [58]
Large cell lymphoma	Serum	<18 U/ml	845 U/ml	Janik [59]
Embryonal carcinoma	Serum	Undetectable	100–270 U/ml	Latza [60]
Osteosarcoma	Serum	8.7 U/ml	35.5 U/ml	Holz [61]
Ewing sarcoma	Serum	8.7 U/ml	52.9 U/ml	Holz [61]

molecules (Online Resource 1 and 2), thus opening up important new perspectives in stratified medicine.

In practice, changes in the level of sCD30 in the cellular environment (serum, tissue, or tumor microenvironment) of peripheral blood mononuclear cells, monocytes, and dendritic cells can be used as a biomarker for changes in cytokine production pathways responsible for regulating differentiation of Th cells into Th1, or Th2, or Th3 or Th17 cells (Fig. 1 and Online Resource 1). sCD30 levels within physiological ranges is a positive prognostic biomarker as it reflects homeostasis in the immunological system and therapeutic response. A significant increase in sCD30 levels, on the other hand, is a negative biomarker, indicating immunological deficit and therapeutic risk (Fig. 2). However, both Trx1 and sCD30 can influence the ability of CD30R to mediate the activation of intracellular signaling by selectively inhibiting interaction with CD30L (Fig. 1 and Online Resource 1): Trx1 by catalytically changing RCD30 structure and sCD30 by closely binding to CD30L and blocking its binding to RCD30. Therefore, both components need to be taken into consideration if they are to be effectively used as biomarkers. Changes in levels of Trx1 and sCD30 are the functional extracellular biomarkers of the new Trx1/CD30 target, and the levels of Treg/Th1/Th17 cytokine production are the functional biomarkers of intracellular pathways (Fig. 3). In addition, being able to manipulate their roles in pathological processes may well represent a non-invasive means of redirecting the physiological system toward a beneficial immunological and therapeutic response (Online Resource 2).

In conclusion, these results indicate that the Trx1/CD30 system not only represents a dual prognostic and stratification biomarker for clinical diagnosis and therapeutic risk/benefit indices, but that it also has the potential to be a dual target in translational research into the pharmacological modulation of multiple redox and immunological pathways aimed at the simultaneous optimization of the regulation of redox and immune system functions.

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