Review

Diverse Functions of VDUP1 in Cell Proliferation, Differentiation, and Diseases

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Vitamin D_3 up-regulated protein 1 (VDUP1) is a multifunctional protein involved in maintaining cellular homeostasis. VDUP1 is induced by a variety of stresses. Inversely, VDUP1 is often reduced in various tumor tissues and cell lines. Over-expression of VDUP1 inhibits cell proliferation through cell cycle arrest. VDUP1 interacts with thioredoxin (Trx) and negatively regulates the expression and antioxidant function of Trx which is involved in redox regulation. VDUP1$^{-/-}$ mice are more susceptible to carcinogenesis than wild-type mice and are defective in establishing immune system including the development and function of natural killer cells. Furthermore, VDUP1$^{-/-}$ mice show impaired Kreb cycle-mediated fatty acid utilization. In this review, we have discussed the multifunctional roles of VDUP1 in diverse cellular responses, in particular its relation to proliferation, apoptosis, differentiation, and diseases such as cancer and stress-related diseases. *Cellular & Molecular Immunology*. 2007; 4(5):345-351.

Key Words: VDUP1, thioredoxin, proliferation, immune cell

Vitamin D_3 up-regulated protein 1 (VDUP1) was originally identified in HL60 cells stimulated with 1,25-$(OH)_2D_3$ and was reported to bind the reduced thioredoxin (Trx) by yeast-two hybrid assay, hence it is thought to be a negative regulator of Trx (1-3). VDUP1 directly interacts with redox active domain of Trx through two cysteine residues which are catalytic active center of Trx. Therefore, VDUP1 blocks the reducing activity of Trx and inhibits the interaction between Trx and other factors, such as ASK-1 and PAG (1, 3). VDUP1 is induced when the cell cycle is blocked by various growth arrest stimuli (3). Over-expression of VDUP1 inhibits the proliferation of tumor cells and cell cycle progress (4). Clinical data also showed that VDUP1 expression is strongly associated with tumorigenesis and is significantly reduced in tumor tissues including breast and lung cancers. These findings suggested that VDUP1 is a novel tumor suppressor (4). Besides, VDUP1 is a major messenger in intracellular physiological processes triggered by various stress stimuli, and plays a crucial role in fatty acid utilization (5). Recently, genetic and metabolic data have revealed that VDUP1 is involved in human metabolism, especially in lipid metabolism and plays a critical role in the development and function of natural killer (NK) cells (6). Collectively, these data suggest that VDUP1 has multifunctional roles in many cellular responses as depicted in Figure 1.

VDUP1 and proliferation

VDUP1 expression is regulated by environmental conditions and its expression affects the cell growth. VDUP1 is up-regulated by various stresses including H_2O_2, irradiation, heat shock, serum starvation, and transforming growth factor-β (TGF-β) (3, 4). In addition, anticancer and anti-proliferative reagents such as 5-fluorouicil, anisomycin, dexamethasone, and SAHA known as a potent inhibitor of histone deacetylases (HDACs), increased VDUP1 expression in cancer cells (7, 8). Meanwhile, its expression instead was reduced in chemically induced rat mammary tumors and ferric nitrilotriacetate (Fe-NTA)-induced renal cancer model of rats (9, 10). Fe-NTA-induced VDUP1 was associated with the increase of proliferating cell nuclear antigen in renal cell carcinomas (RCCs), suggested that the loss of VDUP1 is essential for cellular proliferation in RCCs (9, 10).

Over-expression of VDUP1 inhibited the activity of Trx, eventually leading to the inhibition of tumor cell proliferation (11). Meanwhile, platelet derived growth factor suppressed VDUP1 expression in parallel with the increase of Trx activity (12). Trx stimulates the growth of normal and cancer cells (13), inhibits apoptosis *via* apoptosis signaling kinase-1

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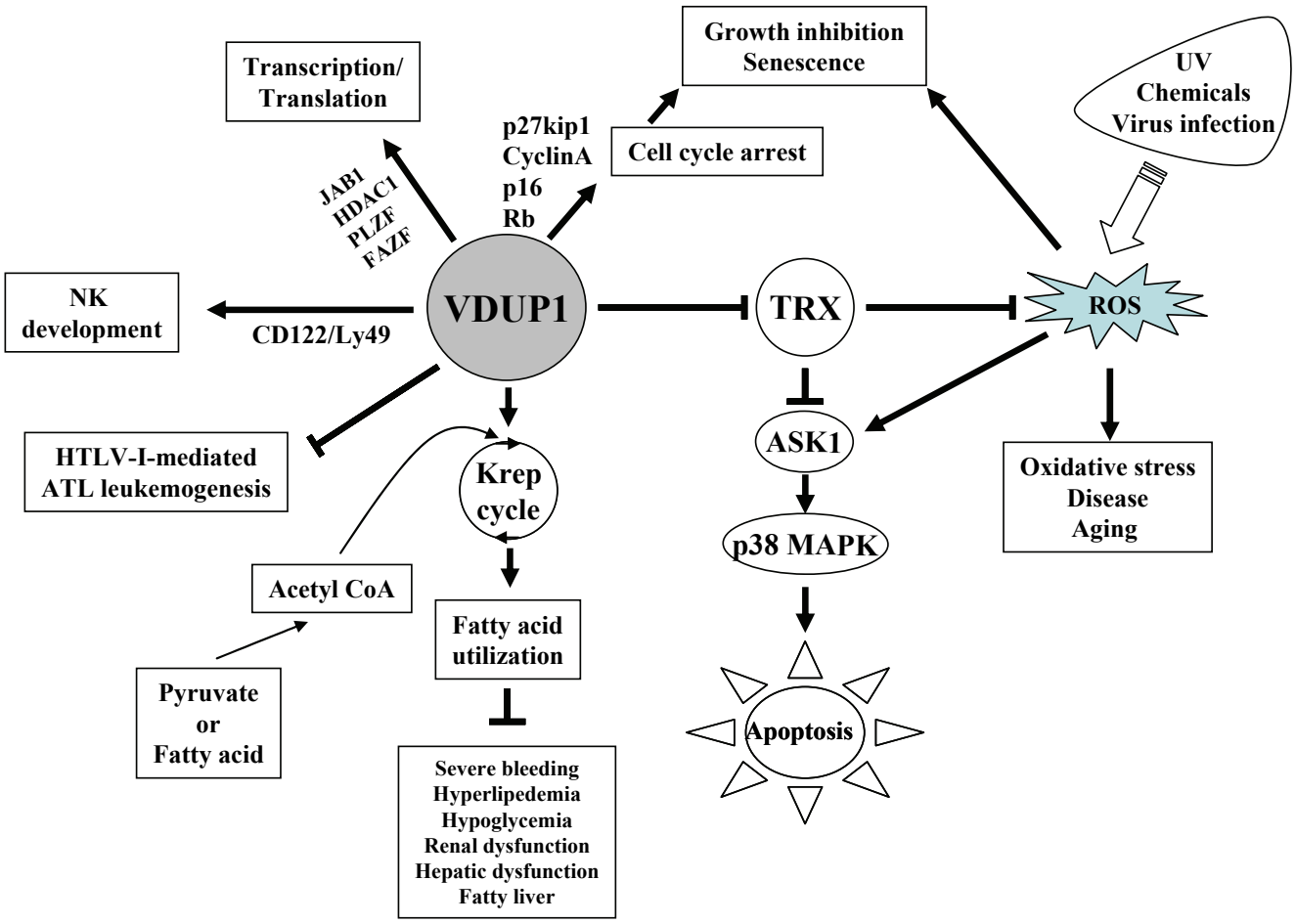

Figure 1. A scheme of multifunctional roles of VDUP1 in diverse cellular phenomenon. VDUP1 is involved in a variety of cellular functions including growth inhibition, transcriptional regulation, NK development, lipid metabolism through inhibition of Trx-mediated antioxidant function and modulating other molecules. NK, natural killer; TRX, thioredoxin; ROS, reactive oxygen species; ASK1, apoptosis signal-regulating kinase 1; JAB1, jun activating binding protein 1; HDAC1, histone deacetylase 1; PLZF, promyelocytic leukemia zinc finger; FAZF, fanconi anemia zinc finger.

(ASK-1) and PTEN which is involved in transducing PI3-kinase signaling (14), and decreases the survival of patients (15-17). In addition, Trx enhances transcriptional activity regulated by AP-1 and p53 (18). These findings suggest that VDUP1 regulates cell proliferation by inhibiting Trx activity.

In addition, VDUP1 is involved in cell cycle regulation. The expression of cyclin A, an important regulator in mitotic cell cycle, is inhibited by VDUP1 at transcription level, leading to cell-cycle arrest at G_0/G_1 (4). VDUP1-mediated cell cycle arrest is also associated with the regulation of cyclin-dependent kinases including p16 and $p27^{kip1}$(11, 19). The p16 interacted with cyclin-dependent kinases (CDK) 4 and 6, and thereby inhibited the G_1-S transition through Rb which is a growth suppressive phosphoprotein and phosphorylated by CDK 4 and 6. When VDUP1 was over-expressed in HTLV-I-positive T cells, significant increase of p16 expression was observed, thereby preventing cells from entering S phase through the reduction of phosphorylation of Rb (11). This result suggested that VDUP1 is crucial for the growth regulation of T cells. $p27^{kip1}$, another cell cycle regulator, is also associated with VDUP1-mediated cell cycle arrest (20, 21). Fibroblasts from VDUP1-deficient mice proliferated more rapidly compared with those from wild-type mice along with the reduced expression of $p27^{kip1}$ (19). It was reported that the stability of $p27^{kip1}$ was regulated by JAB1 (22). Recent data showed that VDUP1 interacted with JAB1 and suppressed JAB1-mediated $p27^{kip1}$ degradation and cell proliferation (19). Reduction of VDUP1 expression in tumors gives rise to increase in the cell proliferation by reducing the stability of $p27^{kip1}$ protein (19).

VDUP1 and apoptosis

Apoptosis is a defense mechanism for the aberrant regulation of cell proliferation and tumor promotion. Although the roles

of VDUP1 in apoptosis regulation have not fully been understood yet, there is accumulating evidence for the involvement of VDUP1 in apoptosis; up-regulation of VDUP1 expression was accompanied by the induction of apoptosis triggered by various agents such as anisomycin, oxidative stress, dexamethasone, PPARγ, calcium influx, potassium ion, and SAHA (7, 23-26). However, the effects of VDUP1 on apoptosis were reported to be dependent on cell types. For example, over-expression of VDUP1 was not sufficient to induce apoptosis in SNU gastric cancer cells, 293 cells (4) and MCF-7 breast cancer cells (11). On the other hand, ectopic expression of VDUP1 induced the apoptosis in WEHI7.2 T cell lymphoma and primary rat cardiomycyte (23, 25). These results suggested that the putative apoptotic roles of VDUP1 were dependent on cell types and oxidative stresses (4).

Recently, a mechanism by which VDUP1 modulates apoptosis has been proved. VDUP1 inhibited the interaction between Trx and ASK1, and the increased ASK1-induced apoptosis (27). ASK1 is a regulatory protein in maintaining cell cycling and proliferation, and modulates the activity of the mitogen-activated protein kinase kinase kinase (MAPKKK) (27). ASK1 activated by various stresses induces apoptosis through the activation of JNK and p38 MAPK pathways (28, 29). Cellular ASK1 level is regulated by ubiquitination and degradation of ASK1, which is related to the direct binding of its N-terminal region to the reduced form of Trx (30). Collectively, the apoptosis induction by VDUP1 might be one of central roles in maintaining cellular homeostasis through its action as a physical regulator of Trx and ASK1 (27).

VDUP1 and differentiation

Although VDUP1 is mainly distributed in immune organs such as thymus and spleen (3), the roles in immune system are not fully understood. Our recent study suggests that VDUP1 plays a critical role in the development and function of natural killer (NK) cells, the component of the innate immune system is able to quickly respond to viral infections and tumors (6). There was a severe reduction in NK cell population and cytotoxicity of VDUP1$^{-/-}$ mice than those of wild-type mice, whereas little changes in T and B cell population. Gene expression of CD122 and Ly49 receptors, markers for NK differentiation, was also decreased in VDUP1$^{-/-}$ mice. *In vitro* NK cell differentiation studies showed that CD122 expression was reduced in VDUP1$^{-/-}$ mice than that in wild-type mice during the development of bone marrow (BM) derived-hematopoietic stem cells (HSCs). In addition, immumohistochemistry studies showed that diffuse hyperplasia of lymphoid tissue containing a large germinal center in the ileum existed only in VDUP1$^{-/-}$ mice, and NK population in lamina propria of ileum was significantly decreased in VDUP1$^{-/-}$ mice than that in wild-type mice. Furthermore, NK-mediated tumor rejection in VDUP1$^{-/-}$ mice was much less efficient than that of wild-type mice.

VDUP1 seems to regulate NK cell differentiation through inducing CD122 expression. CD122 expression was much reduced in VDUP1$^{-/-}$ mice than that of wild-type mice. VDUP1 increased the promoter activity of CD122, indicating that VDUP1 increases CD122 expression and NK cell differentiation. Molecular mechanisms for VDUP1-mediated CD122 expression will be studied further.

Our study also suggests that the reduced cytotoxicity of NK cells resulted from the depletion of NK cell population in VDUP1$^{-/-}$ mice may be related to CD8^{+} cells. Especially, CD8^{+} cells of both lymph node and spleen were reduced in VDUP1$^{-/-}$ mice, but thymic CD8^{+} cells were not changed. Recently, besides direct effect of NK cells on a pathogen or tumor, NK cells were reported to promote the activity of other immune cells including CTLs, dendritic cells (DCs), Th1 cells, and macrophages (31-34). Collectively, the depletion of NK cells in VDUP1$^{-/-}$ mice reduces the CTL activity and the population of CD8^{+} cells.

In addition, VDUP1 deficiency also affected intestinal hyperplasia and tumor rejection. Depletion of NK cells was related to many diseases including systemic lupus erythematosus, intestinal hyperplasia and tumors (35-38). In fact, intraepithelial lymphocytes (IELs) known as a key effector in mucosal immunity (39) as well as lamina propria lymphocytes (LPLs) were severely increased in small intestine of VDUP1$^{-/-}$ mice. These facts provide that the regulatory roles of VDUP1 in growth inhibition and cell cycle arrest may be implicated in the increase of immune subsets such as IEL and LPL (4, 11).

There is another possible assumption for the involvement of VDUP1 in protecting against Trx-related infectious and inflammatory disorders. Elevated expression of Trx in histology of various human tissues were observed, particularly in thymus (40, 41). These Trx-producing thymic cells have the morphology of interdigitating DCs, which are involved in antigen presenting in immune system and host defense mechanism. These results suggest that Trx has certain roles in immune, endocrine and nervous systems (42, 43). Therefore, VDUP1 may serve as an endogenous negative modulator of Trx in cellular processes including differentiation and activation of immune system.

VDUP1 and diseases

Cancer

Cancer has been represented as an uncontrolled cell growth. Normal cells grow and die repeatedly in a scheduled program, but cancer cells grow in the deregulated cellular program. The dysfunction of growth regulation is deeply related to genetic mutation caused by something to damage DNA or to stimulation of mitosis caused by hormones, chronic tissue injury, oxidizing agents, and viruses. Especially, mutations in cellular oncogenes and tumor suppressor genes, as well as epigenetic alterations are crucial for promoting tumorigenesis (44, 45). These genetic alterations affect proliferation, differentiation, and apoptosis in the process of tumor formation (46).

VDUP1 is known as a tumor suppressor protein (4, 19, 47). Its expression is reduced in human breast, lung, colon tumor tissues, and various tumor cell lines, as well as rat mammary tumor (9, 10). The locus of VDUP1 gene, mouse chromosome 3 that is syntenic with a region of human chromosome lq21, is closely related to high frequency of genomic instability in human tumors (48). The enforced expression of VDUP1 inhibited the proliferation of cancer cells including stomach cancer, promyelocytic leukemia (4), cardiomyocyte (25), and suppressed tumor growth and metastasis in transplantation models (47). Recent data indicated that VDUP1-deficiency induced the development and progression of malignancy, especially hepatocellular carcinoma (49).

Cancer promotion is also deeply related to the deregulated cell cycle. VDUP1 expression was found to be up-regulated in cell-cycle-arrested cells, indicating that VDUP1 is related to cell-cycle regulation (4). VDUP1 affects the cell cycle through the association with diverse cell cycle regulators containing cyclin A (50), p16 (11), and $p27^{kip1}$ (11, 19). These proteins are involved in tumor progression and are often used as markers for tumor prognosis in deregulated states (20, 21). Especially, loss of VDUP1 expression in HTLV-1-infected T cells accompanying with the decrease of p16 is one of the key events involved in the multistep progression of adult T-cell leukemogenesis (11). The stability of $p27^{kip1}$ was regulated by JAB1-VDUP1 interaction (19). The reduction of VDUP1 expression in tumor cells gives rise to low stability of $p27^{kip1}$ protein, which plays a key role in tumorigenesis (19).

Various tumor cells are known to generate ROS, contributing the tumor cells to transform normal cells and to advance metastases (51). These pro-oxidant states can promote tumor cells to neoplastic proliferation (52). In melanoma, endogenous ROS autocrinically stimulates constitutive activation of NF-κB, and it ultimately provokes tumor growth (53, 54). In addition, antioxidants including *N*-acetyl cysteine (NAC), catalase, and over-expression of MnSOD suppressed the tumor cell proliferation *in vitro* and *in vivo* (53-55). Down-regulation of VDUP1 expression by gene silencing in melanoma cell reduced the ROS production and expression of Fas ligand, which are related to tumor cell survival (56).

Stress-related disease

VDUP1 is a major messenger of intracellular physiological processes triggered by various stress stimuli (3, 4, 12, 25, 56, 57). VDUP1 is significantly expressed in response to acute myocardial ischemia in rat hearts. In addition, cardiomyocyte survivals upon oxidative stress and acute myocardial ischemia increased by knock-out of VDUP1 gene. These evidences collectively suggest that VDUP1 participates in regulatory roles in cardiac physiology and cell survival process during oxidative stress (25, 27). In contrast, over-expression of VDUP1 decreased hypertrophy after aortic constriction, implying that VDUP1 is closely related to the development of pressure-overload cardiac hypertrophy mediated by Trx (58, 59). These data provide the evidence that VDUP1 regulates the function of Trx in scavenging stress-mediated ROS (58).

Redox regulation associated with reduction and oxidation has been considered as an important phenomenon in controlling cellular oxidative stress. The involvement of VDUP1 in redox regulation was first suggested by the identification of VDUP1 as a binding partner for Trx which is one of the major components of the thiol reducing system and plays multiple roles in cellular process in proliferation, apoptosis, and gene expression (1). Over-expression of VDUP1 increased the level of ROS in fibroblast (58). In contrast, VDUP1-deficient mice were decreased at the level of intracellular ROS (6).

Since ROS are often considered as toxic stresses against cells, controlling the redox system in response to ROS is very important in regulating the cellular processes such as proliferation, gene expression, cell cycle and apoptosis (60-63). Trx plays a protective role against oxidative stress and regulates signal transduction (14, 64, 65), modulates the DNA-binding activities of transcription factors such as NF-κB and AP-1 in the nucleus (66), regulates stress-mediated ASK level by ubiquitination and degradation of ASK1 through direct binding of its N-terminal region to the reduced form of Trx (30). The function of VDUP1 as a negative regulator of Trx is associated with the fact that VDUP1 competes with other proteins for binding to Trx. For example, over-expression of VDUP1 reduced the interaction of Trx with PAG or ASK-1, causing cells to become more sensitive to oxidative stress (3). PAG is a thiol-specific antioxidant that reduces hydrogen peroxide when Trx is present as an immediate electron donor (67, 68), and the activity of ASK-1 is induced by ROS due to the dissociation with Trx (14). Thus, the interference of VDUP1 on the interaction between Trx and PAG or ASK-1 makes the cells more sensitive to oxidative stress.

Metabolic diseases

Recently, genetic and metabolic data have provided that VDUP1 plays a crucial role in human metabolism, especially in lipid metabolism. VDUP1 has been found as a highly glucose-responsive gene in human intact pancreatic islets and breast cancers derived from cell lines by microarray analysis (69, 70). Recent data showed that glucose treatment directly stimulates the expression of VDUP1 *via* carbohydrate response element (ChoRE) existing in VDUP1 promoter (71). This up-regulation of VDUP1 by glucose leads to elicit glucotoxicity and β-cell apoptosis.

Bodnar et al. identified that a mutant mouse strain, HcB-19/deem (HcB-19) that had the characteristics of familial combined hyperlipidemia (FCHL) including hyper-triglyceridemia and hypercholesterolemia, elevated plasma apolipoprotein B and increased the secretion of triglyceride-rich lipoprotein (72, 73). This mutant mouse contains genetic deficiency which has a spontaneous mutation at a locus, Hyplip1, on distal chromosome 3 in a region sytenic with a 1q21-q23 FCHL. Interestingly, nonsense mutation in VDUP1 gene producing N-terminal truncation of the protein has been found in a spontaneous hyperlipidemia mouse strain, HcB-19.

These facts suggest that VDUP1 could be a causative gene for FCHL in mouse (72, 73). Meanwhile, in other case, upstream stimulatory factor 1 (USF1) of VDUP1 is also suggested as an element involved in FCHL (74-76).

Functions of VDUP1 in hyperlipidemia as well as genetic variations of VDUP1 are related to hyperglycemia which has been known to exacerbate β-cell failure and the defect of skeletal muscle glucose uptake *via* a process termed glucose toxicity (76, 77). Since hyper-oxidative stress condition contributes to the development of vascular complications in diabetes, antioxidative function of Trx is considered as a key factor in hyperglycemia-induced oxidative stress. Moreover, VDUP1, a binding partner for the Trx protein, provides a clue to solve the regulating mechanism in diabetes mellitus. Thereafter, VDUP1 expression was increased, and Trx activity was reduced in vascular of diabetic animals. These observations provide the possibility that the induction of VDUP1 in hyperglycemia may affect the susceptibility of Trx to ROS-scavenging system following the increase of oxidative stress by inhibiting Trx activity.

In VDUP1$^{-/-}$ mice model, Oka et al. showed that fatal abnormalities including the reduced survival rate, sever bleeding, dyslipidemia, fatty liver, hypoglycemica, and hepatic- and renal-dysfunction were induced under fasting conditions in VDUP1$^{-/-}$ mice although these mutant mice were viable and fertile under normal housing conditions (5). These symptoms are similar to fatty acid utilization disorders, suggesting that VDUP1 plays a crucial role in fatty acid utilization. In addition, compared with wild-type mice, VDUP1$^{-/-}$ mice showed the facts that Krebs cycle-mediated fatty acid utilization was deregulated by the increased levels of plasma ketone bodies, pyruvate, and lactate. These fatal failures of fatty acid utilization share common characteristics in metabolic feature of Reye-like syndrome, a metabolic syndrome due to the disorders of mitochondrial fatty acid β-oxidation including acute encephalopathy, hepatic dys-function, and fatty infiltration of the visceral organs (78), and therefore, the VDUP1$^{-/-}$ mouse might be used as an animal model for disorder such as Reye syndrome. Moreover, acetyl-coA catabolism was deregulated by the defect of β-oxidation in VDUP1$^{-/-}$ mice, defined as the elevated serum levels of ketone bodies which are converted from the excess amounts of acetyl-CoA (79). Since carcinogenesis is also associated with the deregulation of basic energy metabolism, the increase of glycolysis and reduction of Krebs cycle in VDUP1$^{-/-}$ mice cause the metabolic change-induced carcinogenesis, and thus VDUP1 might be suggested as a tumor suppressor (79).

Conclusion

VDUP1 is a stress-response molecule, originally identified in HL60 cells stimulated with 1,25-$(OH)_2D_3$ (80). VDUP1 binds the reduced Trx and inhibits its reducing activity, suggesting its role in redox regulation. Collectively, since the modulation of cellular redox state by Trx is important in pathogenesis and various ROS-induced cellular phenomena containing proliferation, apoptosis, tumorigenesis, metastasis, and diabetes, VDUP1 might decrease the protective roles of Trx against oxidative stress. VDUP1 has the typical characteristics of tumor suppressor protein. VDUP1 expression is reduced in many tumor cells, and cell cycle arrest is induced by the enforced expression of VDUP1. VDUP1 inhibited the transcription of cyclinA2 through the association with other corepressors (4). Inversely, VDUP1 also interacted with coactivators including Jab1, and induced the gene expression of several signaling molecules independent of Trx activity. These selective interactions between VDUP1 and corepressor or coactivator confer the ability to regulate target gene expression positively or negatively depending on the environmental stimuli. Recently, using VDUP1$^{-/-}$ mice, immunological relevance was demonstrated by the fact that VDUP1 was required for NK development, and moreover, VDUP1 has been strongly suggested as a deregulator of basic energy metabolism utilizing fatty acid pathways.

Taken together, VDUP1 has been revealed as a multifunctional protein and further studies will be highlighted on the diagnostic and therapeutic potential for hard-to-cure human diseases by modulating the functions of VDUP1.

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References

1. Nishiyama A, Matsui M, Iwata S, et al. Identification of thioredoxin-binding protein-2/vitamin D(3) up-regulated protein 1 as a negative regulator of thioredoxin function and expression. J Biol Chem. 1999;274:21645-21650.
2. Yamanaka H, Maehira F, Oshiro M, et al. A possible interaction of thioredoxin with VDUP1 in HeLa cells detected in a yeast two-hybrid system. Biochem Biophys Res Commun. 2000;271: 796-800.
3. Junn E, Han SH, Im JY, et al. Vitamin D3 up-regulated protein 1 mediates oxidative stress *via* suppressing the thioredoxin function. J Immunol. 2000;164:6287-6295.
4. Han SH, Jeon JH, Ju HR, et al. VDUP1 upregulated by TGF-β1 and 1,25-dihydorxyvitamin D3 inhibits tumor cell growth by blocking cell-cycle progression. Oncogene. 2003;22:4035-4046.
5. Oka S, Liu W, Masutani H, et al. Impaired fatty acid utilization in thioredoxin binding protein-2 (TBP-2)-deficient mice: a unique animal model of Reye syndrome. FASEB J. 2006;20: 121-123.
6. Lee KN, Kang HS, Jeon JH, et al. VDUP1 is required for the development of natural killer cells. Immunity. 2005;22:195-208.
7. Butler LM, Zhou X, Xu WS, et al. The histone deacetylase inhibitor SAHA arrests cancer cell growth, up-regulates thioredoxin-binding protein-2, and down-regulates thioredoxin. Proc Natl Acad Sci U S A. 2002;99:11700-11705.

8. Takahashi Y, Nagata T, Ishii Y, Ikarashi M, Ishikawa K, Asai S. Up-regulation of vitamin D3 up-regulated protein 1 gene in response to 5-fluorouracil in colon carcinoma SW620. Oncol Rep. 2002;9:75-79.
9. Dutta KK, Nishinaka Y, Masutani H, et al. Two distinct mechanisms for loss of thioredoxin-binding protein-2 in oxidative stress-induced renal carcinogenesis. Lab Invest. 2005; 85:798-807.
10. Yang X, Young LH, Voigt JM. Expression of a vitamin D-regulated gene (VDUP-1) in untreated- and MNU-treated rat mammary tissue. Breast Cancer Res Treat. 1998;48:33-44.
11. Nishinaka Y, Nishiyama A, Masutani H, et al. Loss of thioredoxin-binding protein-2/vitamin D3 up-regulated protein 1 in human T-cell leukemia virus type I-dependent T-cell transformation: implications for adult T-cell leukemia leukemogenesis. Cancer Res. 2004;64:1287-1292.
12. Schulze PC, De Keulenaer GW, Yoshioka J, Kassik KA, Lee RT. Vitamin D3-upregulated protein-1 (VDUP-1) regulates redox-dependent vascular smooth muscle cell proliferation through interaction with thioredoxin. Circ Res. 2002;91:689-695.
13. Powis G, Mustacich D, Coon A. The role of the redox protein thioredoxin in cell growth and cancer. Free Radic Biol Med. 2000;29:312-322.
14. Saitoh M, Nishitoh H, Fujii M, et al. Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. EMBO J. 1998;17:2596-2606.
15. Lincoln DT, Ali Emadi EM, Tonissen KF, Clarke FM. The thioredoxin-thioredoxin reductase system: over-expression in human cancer. Anticancer Res. 2003;23:2425-2433.
16. Raffel J, Bhattacharyya AK, Gallegos A, et al. Increased expression of thioredoxin-1 in human colorectal cancer is associated with decreased patient survival. J Lab Clin Med. 2003;142:46-51.
17. Tome ME, Johnson DB, Rimsza LM, et al. A redox signature score identifies diffuse large B-cell lymphoma patients with a poor prognosis. Blood. 2005;106:3594-3601.
18. Akamatsu Y, Ohno T, Hirota K, Kagoshima H, Yodoi J, Shigesada K. Redox regulation of the DNA binding activity in transcription factor PEBP2. The roles of two conserved cysteine residues. J Biol Chem. 1997;272:14497-14500.
19. Jeon JH, Lee KN, Hwang CY, Kwon KS, You KH, Choi I. Tumor suppressor VDUP1 increases p27(kip1) stability by inhibiting JAB1. Cancer Res. 2005;65:4485-4489.
20. Lloyd RV, Erickson LA, Jin L, et al. p27kip1: a multifunctional cyclin-dependent kinase inhibitor with prognostic significance in human cancers. Am J Pathol. 1999;154:313-323.
21. Masciullo V, Susini T, Zamparelli A, et al. Frequent loss of expression of the cyclin-dependent kinase inhibitor p27(Kip1) in estrogen-related Endometrial adenocarcinomas. Clin Cancer Res. 2003;9:5332-5338.
22. Tomoda K, Kubota Y, Kato J. Degradation of the cyclin-dependent-kinase inhibitor p27Kip1 is instigated by Jab1. Nature. 1999;398:160-165.
23. Wang Z, Rong YP, Malone MH, Davis MC, Zhong F, Distelhorst CW. Thioredoxin-interacting protein (txnip) is a glucocorticoid-regulated primary response gene involved in mediating glucocorticoid-induced apoptosis. Oncogene. 2006; 25:1903-1913.
24. Saitoh T, Tanaka S, Koike T. Rapid induction and Ca^{2+} influx-mediated suppression of vitamin D3 up-regulated protein 1 (VDUP1) mRNA in cerebellar granule neurons undergoing apoptosis. J Neurochem. 2001;78:1267-1276.
25. Wang Y, De Keulenaer GW, Lee RT. Vitamin D_3-up-regulated protein-1 is a stress-responsive gene that regulates cardiomyocyte viability through interaction with thioredoxin. J Biol Chem. 2002;277:26496-26500.
26. Billiet L, Furman C, Larigauderie G, et al. Enhanced VDUP-1 gene expression by PPARγ agonist induces apoptosis in human macrophage. J Cell Physiol. 2007; in press.
27. Xiang G, Seki T, Schuster MD, et al. Catalytic degradation of vitamin D up-regulated protein 1 mRNA enhances cardiomyocyte survival and prevents left ventricular remodeling after myocardial ischemia. J Biol Chem. 2005;280:39394-39402.
28. Tobiume K, Matsuzawa A, Takahashi T, et al. ASK1 is required for sustained activations of JNK/p38 MAP kinases and apoptosis. EMBO Rep. 2001;2:222-228.
29. Song JJ, Lee YJ. Differential role of glutaredoxin and thioredoxin in metabolic oxidative stress-induced activation of apoptosis signal-regulating kinase 1. Biochem J. 2003;373:845-853.
30. Liu Y, Min W. Thioredoxin promotes ASK1 ubiquitination and degradation to inhibit ASK1-mediated apoptosis in a redox activity-independent manner. Circ Res. 2002;90:1259-1266.
31. Mocikat R, Braumuller H, Gumy A, et al. Natural killer cells activated by MHC class I^{low} targets prime dendritic cells to induce protective CD8 T cell responses. Immunity. 2003;19: 561-569.
32. Barber MA, Zhang T, Gagne BA, Sentman CL. NK cells negatively regulate antigen presentation and tumor-specific CTLs in a syngeneic lymphoma model. J Immunol. 2007;178: 6140-6147.
33. Geldhof AB, Van Ginderachter JA, Liu Y, Noel W, Raes G, De Baetselier P. Antagonistic effect of NK cells on alternatively activated monocytes: a contribution of NK cells to CTL generation. Blood. 2002;100:4049-4058.
34. Kelly JM, Darcy PK, Markby JL, et al. Induction of tumor-specific T cell memory by NK cell-mediated tumor rejection. Nat Immunol. 2002;3:83-90.
35. Leu RW, Norton TR, Herriott MJ, Ringer DP, Kearns RJ. Suppression of natural killer and lymphocyte functions associated with carcinogen-induced premalignant hyperplastic nodules in rat liver. Cancer Res. 1985;45:3282-3287.
36. Altmann GG, Parhar RS, Lala PK. Hyperplasia of mouse duodenal crypts and its control by NK cells during the initial phase of DMH carcinogenesis. Int J Cancer. 1990;46:695-702.
37. Schattner A, Duggan DB. Natural killer cells and the pathogenesis of systemic lupus erythematosus. Arthritis Rheum. 1984;27:1072-1073.
38. Mickel RA, Kessler DJ, Taylor JM, Lichtenstein A. Natural killer cell cytotoxicity in the peripheral blood, cervical lymph nodes, and tumor of head and neck cancer patients. Cancer Res. 1988;48:5017-5022.
39. Hayday A, Theodoridis E, Ramsburg E, Shires J. Intraepithelial lymphocytes: exploring the Third Way in immunology. Nat Immunol. 2001;2:997-1003.
40. Go T, Isowa N, Hirata T, Yodoi J, Hitomi S, Wada H. Thymic interdigitating cells express thioredoxin (TRX/ADF): an immunohistochemical study of 82 thymus and thymoma samples. Thymus. 1997;24:157-171.
41. Fujii S, Nanbu Y, Konishi I, Mori T, Masutani H, Yodoi J. Immunohistochemical localization of adult T-cell leukaemia-derived factor, a human thioredoxin homologue, in human fetal tissues. Virchows Arch A Pathol Anat Histopathol. 1991;419: 317-326.
42. Tomimoto H, Akiguchi I, Wakita H, Kimura J, Hori K, Yodoi J. Astroglial expression of ATL-derived factor, a human thioredoxin homologue, in the gerbil brain after transient global ischemia. Brain Res. 1993;625:1-8.

43. Masutani H, Naito M, Takahashi K, et al. Dysregulation of adult T-cell leukemia-derived factor (ADF)/thioredoxin in HIV infection: loss of ADF high-producer cells in lymphoid tissues of AIDS patients. AIDS Res Hum Retroviruses. 1992;8:1707-1715.
44. Corn PG, El-Deiry WS. Derangement of growth and differentiation control in oncogenesis. Bioessays. 2002;24:83-90.
45. Ross DT, Scherf U, Eisen MB, et al. Systematic variation in gene expression patterns in human cancer cell lines. Nat Genet. 2000;24:227-235.
46. Sherr CJ. The Pezcoller lecture: cancer cell cycles revisited. Cancer Res. 2000;60:3689-3695.
47. Goldberg SF, Miele ME, Hatta N, et al. Melanoma metastasis suppression by chromosome 6: evidence for a pathway regulated by CRSP3 and TXNIP. Cancer Res. 2003;63:432-440.
48. Ludwig DL, Kotanides H, Le T, Chavkin D, Bohlen P, Witte L. Cloning, genetic characterization, and chromosomal mapping of the mouse VDUP1 gene. Gene. 2001;269:103-112.
49. Sheth SS, Bodnar JS, Ghazalpour A, et al. Hepatocellular carcinoma in Txnip-deficient mice. Oncogene. 2006;25:3528-3536.
50. Yam CH, Fung TK, Poon RY. Cyclin A in cell cycle control and cancer. Cell Mol Life Sci. 2002;59:1317-1326.
51. Szatrowski TP, Nathan CF. Production of large amounts of hydrogen peroxide by human tumor cells. Cancer Res. 1991; 51:794-798.
52. Cerutti PA. Prooxidant states and tumor promotion. Science. 1985;227:375-381.
53. Borrello S, De Leo ME, Galeotti T. Defective gene expression of MnSOD in cancer cells. Mol Aspects Med. 1993;14:253-258.
54. Brar SS, Kennedy TP, Whorton AR, et al. Reactive oxygen species from NAD(P)H:quinone oxidoreductase constitutively activate NF-κB in malignant melanoma cells. Am J Physiol Cell Physiol. 2001;280:C659-676.
55. Zhao Y, Xue Y, Oberley TD, et al. Overexpression of manganese superoxide dismutase suppresses tumor formation by modulation of activator protein-1 signaling in a multistage skin carcinogenesis model. Cancer Res. 2001;61:6082-6088.
56. Song H, Cho D, Jeon JH, et al. Vitamin D(3) up-regulating protein 1 (VDUP1) antisense DNA regulates tumorigenicity and melanogenesis of murine melanoma cells *via* regulating the expression of fas ligand and reactive oxygen species. Immunol Lett. 2003;86:235-247.
57. Kim KY, Shin SM, Kim JK, Paik SG, Yang Y, Choi I. Heat shock factor regulates VDUP1 gene expression. Biochem Biophys Res Commun. 2004;315:369-375.
58. Yoshioka J, Schulze PC, Cupesi M, et al. Thioredoxin-interacting protein controls cardiac hypertrophy through regulation of thioredoxin activity. Circulation. 2004;109:2581-2586.
59. Lemmens K, Segers VF, Demolder M, Michiels M, Van Cauwelaert P, De Keulenaer GW. Endogenous inhibitors of hypertrophy in concentric versus eccentric hypertrophy. Eur J Heart Fail. 2007;9:352-356.
60. Armstrong JS, Steinauer KK, Hornung B, et al. Role of glutathione depletion and reactive oxygen species generation in apoptotic signaling in a human B lymphoma cell line. Cell Death Differ. 2002;9:252-263.
61. Liu G, Chen X. The ferredoxin reductase gene is regulated by the p53 family and sensitizes cells to oxidative stress-induced apoptosis. Oncogene. 2002;21:7195-7204.
62. Vaculova A, Hofmanova J, Soucek K, Kovarikova M, Kozubik A. Tumor necrosis factor-α induces apoptosis associated with poly(ADP-ribose) polymerase cleavage in HT-29 colon cancer cells. Anticancer Res. 2002;22:1635-1639.
63. Rosato RR, Grant S. Histone deacetylase inhibitors in cancer therapy. Cancer Biol Ther. 2003;2:30-37.
64. Matsuda M, Masutani H, Nakamura H, et al. Protective activity of adult T cell leukemia-derived factor (ADF) against tumor necrosis factor-dependent cytotoxicity on U937 cells. J Immunol. 1991;147:3837-3841.
65. Nakamura H, Matsuda M, Furuke K, et al. Adult T cell leukemia-derived factor/human thioredoxin protects endothelial F-2 cell injury caused by activated neutrophils or hydrogen peroxide. Immunol Lett. 1994;42:75-80.
66. Schenk H, Klein M, Erdbrugger W, Droge W, Schulze-Osthoff K. Distinct effects of thioredoxin and antioxidants on the activation of transcription factors NF-κB and AP-1. Proc Natl Acad Sci U S A. 1994;91:1672-1676.
67. Jin DY, Chae HZ, Rhee SG, Jeang KT. Regulatory role for a novel human thioredoxin peroxidase in NF-κB activation. J Biol Chem. 1997;272:30952-30961.
68. Noh DY, Ahn SJ, Lee RA, Kim SW, Park IA, Chae HZ. Overexpression of peroxiredoxin in human breast cancer. Anticancer Res. 2001;21:2085-2090.
69. Shalev A, Pise-Masison CA, Radonovich M, et al. Oligonucleotide microarray analysis of intact human pancreatic islets: identification of glucose-responsive genes and a highly regulated TGFβ signaling pathway. Endocrinology. 2002;143:3695-3698.
70. Turturro F, Friday E, Welbourne T. Hyperglycemia regulates thioredoxin-ROS activity through induction of thioredoxin-interacting protein (TXNIP) in metastatic breast cancer-derived cells MDA-MB-231. BMC Cancer. 2007;7:96.
71. Minn AH, Hafele C, Shalev A. Thioredoxin-interacting protein is stimulated by glucose through a carbohydrate response element and induces β-cell apoptosis. Endocrinology. 2005;146:2397-2405.
72. Bodnar JS, Chatterjee A, Castellani LW, et al. Positional cloning of the combined hyperlipidemia gene Hyplip1. Nat Genet. 2002;30:110-116.
73. Hui TY, Sheth SS, Diffley JM, et al. Mice lacking thioredoxin-interacting protein provide evidence linking cellular redox state to appropriate response to nutritional signals. J Biol Chem. 2004;279:24387-24393.
74. Pajukanta P, Lilja HE, Sinsheimer JS, et al. Familial combined hyperlipidemia is associated with upstream transcription factor 1 (USF1). Nat Genet. 2004;36:371-376.
75. Coon H, Singh N, Dunn D, et al. TXNIP gene not associated with familial combined hyperlipidemia in the NHLBI Family Heart Study. Atherosclerosis. 2004;174:357-362.
76. van der Vleuten GM, Hijmans A, Kluijtmans LA, Blom HJ, Stalenhoef AF, de Graaf J. Thioredoxin interacting protein in Dutch families with familial combined hyperlipidemia. Am J Med Genet A. 2004;130:73-75.
77. van Greevenbroek MM, Vermeulen VM, Feskens EJ, et al. Genetic variation in thioredoxin interacting protein (TXNIP) is associated with hypertriglyceridaemia and blood pressure in diabetes mellitus. Diabet Med. 2007;24:498-504.
78. Glasgow JF, Middleton B. Reye syndrome--insights on causation and prognosis. Arch Dis Child. 2001;85:351-353.
79. Oka SI, Masutani H, Liu W, et al. Thioredoxin-binding protein-2 (TBP-2)-like inducible membrane protein (TLIMP) is a novel Vitamin D3 and PPAR-γ ligand target protein that regulates PPAR-γ signaling. Endocrinology. 2005;147:733-743.
80. Chen KS, DeLuca HF. Isolation and characterization of a novel cDNA from HL-60 cells treated with 1,25-dihydroxyvitamin D-3. Biochim Biophys Acta. 1994;1219:26-32.