Exp Oncol 2006
28, 4, 258–262

REVIEW

Experimental ONCOLOGY

ZINC RIBBON DOMAIN CONTAINING 1 PROTEIN: MODULATOR OF MULTIDRUG RESISTANCE, TUMORIGENESIS AND CELL CYCLE

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Zinc ribbon domain containing 1 (ZNRD1) gene encoding a protein consisting of two zinc ribbon domains was recently cloned from the human HLA locus. So far, ZNRD1 has been found implicated in transcription regulation and might play potential roles in mediating several biological processes, including multidrug resistance, tumorigenesis and cell cycle. This article reviewed these recent findings and provided additional information to support the role of ZNRD1 gene as a novel candidate DNA damage repair related gene.
Key Words: **ZNRD1, gastric cancer, cell cycle, multidrug resistance.**

Zinc ribbon domain containing 1 (ZNRD1) gene encoding a protein consisting of two zinc ribbon domains was cloned from the human HLA locus in 2000 [1]. The zinc ribbon domain was a ubiquitous motif in archaeal and eucaryotic transcription factors, and has been proved to be a functional domain required for biological activities in TFIIS and TFIIB [2–4]. The zinc ribbon domain at the C-terminal of ZNRD1 protein (Cx2Cx24Cx2C) was actually folded as three ß-sheets stabilized by a zinc ion instead of finger-like helices, forming a zinc ribbon structure fitting TFIIS zinc ribbon fold (C-terminal residues 231–281) very well [5]. And the analogous Cys_4 structural motifs were well conserved throughout evolution, including archaea, yeast, drosophila, nematodes, amphibians, and mammals, and might play important roles in promoting cleavage of the nascent transcript and read-through past the block to elongation [6, 7]. Recently, ZNRD1 has been found related to multidrug resistance (MDR), tumorigenesis and cell cycle. Taken together, ZNRD1 might be associated with transcription regulation and might play potential roles in mediating some physiological and pathological functions.

EFFECTS OF ZNRD1 ON MULTIDRUG RESISTANCE

Multidrug resistance (MDR) is a major impediment to the effective chemotherapy of many human malignancies. Molecular investigations discovered diverse mechanisms of MDR, such as extrusion of the drug by cell membrane pumps including P-glycoprotein (P-gp) and multidrug resistance-associated protein (MRP), enhanced drug detoxification, increased DNA damage repair, redistribution of intracellular accumulation of drugs, modification of drug target molecules, suppression of drug-induced apoptosis, up-regulation of lipids and other biochemical alterations [8–12]. Recently, ZNRD1 was found to play important roles in MDR of gastric cancer and leukemia.

ZNRD1 was found over-expressed in the vincristine (VCR)-resistant gastric cancer cell line SGC7901/VCR and the VCR-resistant leukemia cell line HL-60/VCR, compared with their corresponding parental cell lines SGC7901 and HL-60, respectively [13, 14]. To detect the role of ZNRD1 in MDR of tumor cells, the recombinant plasmids containing the full ORF of wild-type ZNRD1 and the siRNA vectors of ZNRD1 were constructed. Using these vectors, the cell models with elevated or decreased ZNRD1 expression were established. MTT assay revealed that ZNRD1 had different effects on drug sensitivity, depending on the drug used. The tumor cells overexpressing ZNRD1 showed a > 12-fold increased resistance to VCR and adriamycin (ADR), and a > 5-fold increased resistance to 5-fluorouracil (5-FU) and cisplatin (CDDP) as compared with control cells ($P < 0.01$) [15]. And the cells with decreased ZNRD1 expression showed significantly increased sensitivity to ADR, VCR (> 4-fold), and 5-FU, CDDP (> 2-fold) [16].

ADR was used as probe to evaluate drug accumulation and retention in the cell models. As the reports showed, up-regulation of ZNRD1 was accompanied with significantly decreased ADR accumulation and retention and increased ADR releasing index. Consistent with this, down-regulation of ZNRD1 led to increased ADR accumulation and retention and decreased ADR releasing index. The results indicated that ZNRD1 had a direct or indirect function of pumping drug out of cells [14], which might result from ZNRD1-induced up-regulation of P-gp. And the P-gp inhibitor, verapamil, could partially reverse the effects of ZNRD1 on drug sensitivity in gastric cancer or leukemia cells, especially for VCR and ADR, suggesting that regulation of P-gp might be one of the mechanisms by which ZNRD1 mediated MDR [16]. Each case of

Received: August 18, 2006.
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Abbreviations used: ADR – adriamycin; CDDP – cisplatin; DHFR – dihydrofolate reductase; 5-FU – 5-fluorouracil; GST – glutathione S transferase; IMPDH2 – inosine monophosphate dehydrogenase 2; MDR – multidrug resistance; MDR1 – multidrug resistance gene 1; MRP – multidrug resistance-associated protein; MTT – 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; MTX – methotrexate; P-gp – P-glycoprotein; pRB – retinoblastoma gene; VCR – vincristine; ZNRD1 – zinc ribbon domain-containing 1.

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P-gp-related MDR has been related to an increased human multidrug resistance gene 1 (MDR1) mRNA level that can be linked either to gene amplification and/or increased gene transcription [17]. It is believed that alterations in MDR1 promoter are important for P-gp function [18]. Co-transfection of cancer cells with MDR1 reporter gene and increasing amounts of ZNRD1 expression vectors resulted in a linear increase in MDR1 promoter activity, suggesting that ZNRD1 might be a transcriptional regulator of the *MDR1* gene. The results of reporter gene assay revealed that putative ZNRD1 binding sites are located among –136–+10 in the MDR-1 promoter [14, 16]. However, the role of ZNRD1 might depend not only on the promoter sequences but also on the association of ZNRD1 with different cofactors. The precise mechanism by which ZNRD1 influences *MDR1* gene expression is the subject of future experimental work.

It should be noted that VCR and ADR are the common substrates for P-gp. But the ZNRD1-related resistance to 5-FU and CDDP couldn't be explained by regulation of P-gp, which suggested that other mechanisms might exist. However, glutathione-S-transferase (GST)-mediated drug-detoxifying system and MRP was not found to be significantly involved in ZNRD1-mediated MDR [14]. Recently, it was proposed that ZNRD1 might mediate the MDR through regulation of apoptosis [19].

Apoptosis is a common pathway that finally mediated the killing functions of anticancer drugs. The gastric cancer cells overexpressing ZNRD1 displayed an impaired capacity to undergo ADR-induced apoptosis, whereas control cells displayed a higher proportion of cells undergoing apoptosis after ADR treatment [19]. Bcl-2 family, including Bcl-2, Bcl-xL, Bax, Bad and Bak, is a rapidly expanding family of proteins involved in apoptosis and responses of tumor cells to chemotherapy [20]. These proteins were believed to modulate apoptosis by forming homodimers or heterodimers with other Bcl-2 family members [21]. A wide variety of human cancers, with poor clinical response to chemotherapy, exhibited high levels of bcl-2 expression. It had been implied that bcl-2 family expression provided resistance to a wide variety of cell death stimuli, including classical chemotherapeutic drugs and radiation [22]. The changed levels of Bcl-2 caused by ZNRD1 might also contribute to suppression effects of ZNRD1 on apoptosis and thus ZNRD1-related MDR of gastric cancer cells.

Another molecule regulated by ZNRD1 is inosine monophosphate dehydrogenase 2 (IMPDH2), which catalyzes the last step in the synthesis of inosine monophosphate. The chemical inhibitors of IMPDH activity are already used in cancer therapy, suggesting the possibility to use them as modulators in combination with methotrexate (MTX), which is an inhibitor of dihydrofolate reductase (DHFR), an enzyme involved in nucleotide synthesis [23]. Decreased IMPDH2 was found responsible for the ZNRD1-mediated tumor resistance to MTX *in vitro*. *In vitro* drug sensitivity analyses also revealed that down-regulation of ZNRD1 expression might decrease the capacity of cells to resist to MTX by inhibiting IMPDH2 [19].

Taken together, ZNRD1 might play certain roles in MDR through P-gp signal pathway and/or cooperation with Bcl-2 and IMPDH2. Further analysis for the mechanism of biological actions of ZNRD1 in MDR might help to further understand the mechanisms of MDR and generate a new approach to reverse MDR.

EFFECTS OF ZNRD1 ON TUMORIGENESIS

Our laboratory has a long-standing interest in the possible role of ZNRD1. We have generated the first mouse monoclonal antibody (clone H6) specific for ZNRD1 protein. With this monoclonal antibody in Western blotting, ZNRD1 was found to be down-regulated in 16 cases of human gastric cancer tissues as compared to the matched adjacent nonneoplastic tissues ($P < 0.001$) [24]. Also, ZNRD1 expression was found to be down-regulated in gastric cancer cell lines (AGS, MKN28, MGC803, SGC7901) compared with normal gastric epithelial cell line (GES) [25]. Immunohistochemical analysis revealed that normal gastric epithelium cells might have a constitutive basal level of ZNRD1 expression for mediating the normal physiologic functions. ZNRD1 staining was found positive in 38 (63%) normal epithelia samples, 51 (81%) gastritis samples, and 7 (8%) adenocarcinoma cases. The expression of ZNRD1 in nontransformed gastric tissues was significantly ($P < 0.001$) higher than that in tumor tissues [26]. Statistical analysis showed that there was no significant correlation between the expression of ZNRD1 and the differentiation, metastasis and Dukes' stage of gastric carcinoma, sex, age, or nationality of patients.

ZNRD1 expression in normal gastric epithelium may be up-regulated in response to various stimuli such as injury or alteration of the environment; for example, upon gastritis, expression level of ZNRD1 was increased with a statistically significant difference ($P < 0.001$). The patterns of ZNRD1 expression, frequently absent in gastric cancer tissues (86/93 (92%)), were typical for tumor suppressor genes [26]. We are now performing the experiments to investigate whether ZNRD1 is related to DNA damage repair system, or whether it carries the possible promoter methylation and mutation. So, ZNRD1 may be an ideal marker of gastric cancer and could be used for a screening purpose.

The involvement of specific genes in tumorigenesis could be confirmed by reconstituting cells null by activity with the respective gene. ZNRD1 cDNA was transfected into AGS gastric cancer cells, which was ZNRD1 null, and three clones overexpressing ZNRD1 were identified. Up-regulation of ZNRD1 has been shown to inhibit the growth of AGS cells *in vitro* and possess anti-carcinogenic activity *in vivo* [25]. What's more, the growth inhibitory rate of AGS transfectants depended on the expression levels of

ZNRD1. Down-regulation of ZNRD1 in normal gastric epithelium cell line GES with siRNA of ZNRD1 could enhance cell growth significantly and promoted cells transition from G1 phase to S phase. However, the cell proliferation of gastric cancer cell line SGC7901, which normally expresses ZNRD1, was hardly affected by up-regulation of ZNRD1, supporting the idea that inactivation of ZNRD1 might be only one of the routes of gastric tumorigenesis [25].

So far, the report about the role of ZNRD1 in tumorigenesis is focused on gastric cancer. These results have indicated that ZNRD1 possessses growth suppressor activity in gastric cancer cells, suggesting that ZNRD1 may play important roles in carcinogenesis of gastric cancer through transcription regulation. Thus, ZNRD1 might be a novel negative modifier in gastric carcinogenesis.

EFFECTS OF ZNRD1 ON CELL CYCLE

It was currently believed that the loss of normal cell cycle control played an important role in the genesis of most, if not all, tumors. Cell cycle progression was governed by the actions of regulators in the eukaryotic cell, including cyclins and CDKs as positive regulators, whereas CKIs served as negative regulators [27]. In normal cells, the proliferation is under strict regulation and these regulators work in concert to ensure a regulated transition from one phase of the cell cycle to the next. In tumor cells, this exquisite balance between the positive and negative regulators is not maintained, thus contributing to the malignant phenotype. Therefore, the cell cycle regulatory proteins have been under intense investigation as the potential molecular targets.

ZNRD1 was found to induce the arrest of AGS cells and the fibroblast cell line NIH3T3 at the G1 phase of the cell cycle as a consequence of inhibition of cyclin D1 expression [25, 26]. Thus, ZNRD1 was assumed to play important roles in G1 checkpoint. Passage through the G1 checkpoint, called the restriction point, allowed cells to progress through the cell cycle in an autonomous and mitogen-independent manner. Cyclins belonging to the D and E families, and their respective kinase partners, CDK4/6 and CDK2, were involved in G1 restriction point control [28]. Cyclin D1/CDK4 complexes governed G1 progression, whereas cyclin E/CDK2 complexes controlled entry into S phase. Cyclins were regulated not only at the transcriptional and translational levels but also by their rate of degradation via the ubiquitin pathway [29]. An additional level of negative control was produced by the expression of CDK inhibitors, including KIPs (p21, p27, p57) and INKs (p15, p16, p18, p19) [30, 31].

As indicated by the results of microarray, up-regulation of ZNRD1 led to decreased CDK4, increased p21, p27 and the retinoblastoma gene (pRB), all of which were proved to play important roles in regulating the G1 to S transition [19]. Cyclin D1 was known to play at least two important roles in facilitating the transition from G_1 phase into S. First, it served as the regulatory subunit of CDK4 and contributed to its stability, allowing the initial phosphorylation of pRb in mid-G_1. Second, it acted in complex with its partner kinase to sequester the cip/kip kinase inhibitors. The effects of ZNRD1-induced reduction of cyclin D1 could be reasonably linked to the mechanisms of the cell cycle arrest both through the resulting inability of unbound CDK4 to phosphorylate pRb and through the potential decrease in the association of cyclin D/CDK4 complexes with p21 and/or p27. With limited sequestration of the cip/kip proteins, increased levels of p27 and/or p21 would be free to associate with, and hence decreased the ability of, cyclin E/CDK2 complexes. The ZNRD1-induced increased expression of hypo-phosphorylated form of pRb might also exert a growth suppressive effect by indirectly influencing transcription of cell-cycle related genes through sequestration of critical transcription factors, such as E2F.

CONCLUSIONS AND FUTURE PERSPECTIVES

ZNRD1 is down-regulated in gastric cancer, and could suppress the growth of gastric cancer cells by cell cycle arrest in G1 phase mediated by down-regulation of cyclin D1. Meanwhile, ZNRD1 might be related to MDR of gastric cancer and leukaemia by regulation of P-gp, Bcl-2, and IMPDH2. It is interesting that ZNRD1 gene expression could not only enhance the proliferative activity of gastric cancer cells after chemothearpeutic drugs treatment, but also suppresses the tumorigenesis activity of gastric cancer cells in animals. These results seemed controversy and brought some philosophical thinks. There might be a balance. As shown in Fig. 1, ZNRD1 was down-regulated in gastric cancer cells, where it was under the balance, so up-regulation of ZNRD1 could reverse the mailgnant phenotype of tumor cells. ZNRD1 was highly expressed in gastric cancer MDR sublines, where it was above the balance, so we have to down-regulate ZNRD1 expression so as to reverse the MDR phenotype of tumor cells. Similar balance might also work for other molecules, for example, DARPP-32 was found highly expressed in gastric cancer but down-regulated in gastric cancer MDR sublines [32].

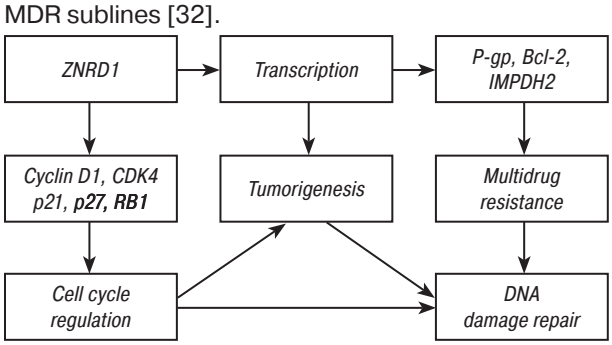

Fig. 1. Functions of ZNRD1. ZNRD1 is down-regulated in gastric cancer, up-regulation of ZNRD1 could reverse the malignant phenotype of tumor cells. ZNRD1 is highly expressed in gastric cancer MDR sublines, so down-regulation of ZNRD1 could reverse the MDR phenotype of tumor cells

It is interesting that ZNRD1 seems to be related to DNA damage repair as following: firstly, ZNRD1 is

a transcription-associated factor, while a number of investigations had shown that transcription factors, such p53, c-Myc, and AP-1 (c-jun and c-fos) [33], are involved in the regulation of stress-inducible genes. Activation of transcription factors by DNA damage would directly enhance the transcription of their downstream genes, which might exert biological functions in cellular response. Secondly, ZNRD1 is found up-regulated in response to treatment with DNA damaging agents (chemotherapeutic drugs), and the expression of ZNRD1 is significantly higher in gastric tissues than in normal gastric epithelial tissues and gastric cancer tissues. Lastly, ZNRD1 might be a cell growth arresting factor, which is commonly induced in response to DNA damage in both bacteria and eukaryotes [34]. Taken together, it could be assumed that after DNA damage, ZNRD1 would be able to regulate cell cycle progression and delicately coordinate with some other gene regulators to ensure the establishment of cellular defense network. However, further studies are required to investigate the role of ZNRD1 in the DNA damage-activated response.

It was becoming increasingly clear that the signals that govern cellular processes, such as entry and exit from the cell cycle, MDR, and DNA damage repair, function in complex regulatory networks rather than simple linear pathways, and that these networks might be wired differently in different cells or tumor types. As shown in Fig. 2, ZNRD1 is found to play roles in MDR, tumorigenesis and cell cycle. The precise mechanisms by which ZNRD1 is involved in these processes, and which of these changes were primary or secondary ones, remained to be elucidated.

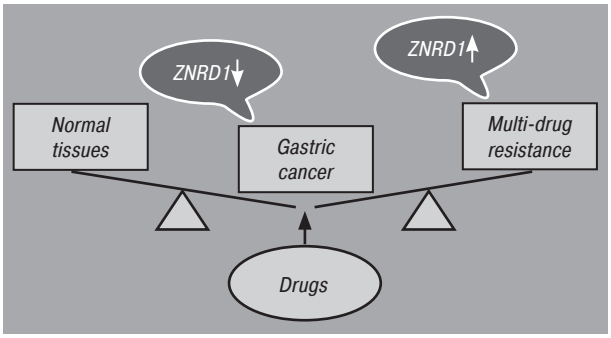

Fig. 2. The advances in ZNRD1 research. ZNRD1 has been found to be implicated in transcription regulation of many genes and might play potential roles in mediating multidrug resistance, tumorigenesis and cell cycle

ACKNOWLEDGMENT

This study was supported in part by grants from the National Scientific Foundation of China (30400203).

REFERENCES

1. **Fan W, Wang Z, Kyzysztof F, Prange C, Lennon G.** A new zinc ribbon gene (ZNRD1) is cloned from the human MHC class I region. Genomics 2000; **63**: 139–41.

2. **Schimanski B, Brandenburg J, Nguyen TN, Caimano MJ, Gunzl A.** A TFIIB-like protein is indispensable for spliced leader RNA gene transcription in Trypanosoma brucei. Nucleic Acids Res 2006; **34**: 1676–84.

3. **Tubon TC, Tansey WP, Herr W.** A nonconserved surface of the TFIIB zinc ribbon domain plays a direct role in RNA polymerase II recruitment. Mol Cell Biol 2004; **24**: 2863–74.

4. **Bushnell DA, Westover KD, Davis RE, Kornberg RD.** Structural basis of transcription: an RNA polymerase II-TFIIB cocrystal at 4.5 Angstroms. Science 2004; **303**: 983–8.

5. **Qian X, Jeon C, Yoon H, Agarwal K, Weiss MA.** Structure of a new nucleic — acid — binding motif in eukaryotic transcriptional elongation factor TFIIS. Nature 1993; **365**: 277–9.

6. **Hansen G, Harrenga A, Wieland B, Schomburg D, Reinemer P.** Crystal structure of full length topoisomerase I from *Thermotoga maritima*. J Mol Biol 2006; **358**: 1328–40.

7. **Okuda M, Tanaka A, Hanaoka F, Ohkuma Y, Nishimura Y.** Structural insights into the asymmetric effects of zinc-ligand cysteine mutations in the novel zinc ribbon domain of human TFIIEalpha for transcription. J Biochem 2005; **138**: 443–9.

8. **Fan D, Zhang X, Chen X, Mou Z, Hu J, Zhou S, Ding J, Wu K.** Bird's-eye view on gastric cancer research of the past 25 years. J Gastroenterol Hepatol 2005; **20**: 360–5.

9. **Penuelas S, Noe V, Ciudad CJ.** Modulation of IMPDH2, survivin, topoisomerase I and vimentin increases sensitivity to methotrexate in HT29 human colon cancer cells. FEBS J 2005; **272**: 696–710.

10. **Abdul-Ghani R, Serra V, Gyorffy B.** The PI3K inhibitor LY294002 blocks drug export from resistant colon carcinoma cells overexpressing MRP1. Oncogene 2006; **25**: 1743–52.

11. **Takahashi S, Ito Y, Hatake K, Sugimoto Y.** Gene therapy for breast cancer. Review of clinical gene therapy trials for breast cancer and MDR1 gene therapy trial in Cancer Institute Hospital. Breast Cancer 2006; **13**: 8–15.

12. **Frelet A, Klein M.** Insight in eukaryotic ABC transporter function by mutation analysis. FEBS Lett 2006; **580**: 1064–84.

13. **Zhao Y, You H, Liu F.** Differentially expressed gene profiles between multidrug resistant gastric adenocarcinoma cells and their parental cells. Cancer Lett 2002; **185**: 211–8.

14. **Hong L, Piao Y, Han Y, Wang J, Zhang X, Du Y, Cao S, Qiao T, Chen Z, Fan D.** ZNRD1 mediates multidrug resistance of leukemia cells through regulation of P-gp and Bcl-2. Zinc ribbon domain-containing 1 (ZNRD1) mediates multidrug resistance of leukemia cells through regulation of P-glycoprotein and Bcl-2. Mol Cancer Ther 2005; **4**: 1936–42.

15. **Piao Y, Chen X, Liu L, Hong L.** Reversion of multidgug resistance in HL-60/VCR cells by down-regulation of bcl-2 with bcl-2 siRNA. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2005; **13**: 1010–3.

16. **Hong L, Ning X, Shi Y, Shen H, Zhang Y, Lan M, Liang S, Wang J, Fan D.** Reversal of multidrug resistance of gastric cancer cells by downregulation of ZNRD1 with ZNRD1siRNA. Br J Biomed Sci 2004; **61**: 206–10.

17. **Labialle S, Gayet L, Marthinet E, Rigal D, Baggetto LG.** Transcriptional regulators of the human multidrug resistance 1 gene, recent views. Biochem Pharmacol 2002; **64**: 943–8.

18. **Potocnik U, Glavac MR, Golouh R, Glavac D.** The role of P-glycoprotein (MDR1) polymorphisms and mutations in colorectal cancer. Pflugers Arch 2001; **442**: 182–3.

19. **Hong L, Qiao T, Han Y, Fan D.** ZNRD1 mediates resistance of gastric cancer cells to methotrexate by regulation of IMPDH2 and Bcl-2. Biochem Cell Biol 2006; **84**: 199–206.

20. **Igney FH, Krammer PH.** Death and anti-death: tumour resistance to apoptosis. Nat Rev Cancer 2002; **2**: 277–88.

21. **Papadopoulos K.** Targeting the bcl-2 family in cancer therapy. Semin Oncol 2006; **33**: 449–56.

22. **Chang HK, Shin MS, Yang HY.** Amygdalin induces apoptosis through regulation of Bax and Bcl-2 expressions in human DU145 and LNCaP prostate cancer cells. Biol Pharm Bull 2006; **29**: 1597–602.

23. **Kennan A, Aherne A, Bowne SJ, Daiger SP, Farrar GJ, Kenna PF, Humphries P.** On the role of IMPDH1 in retinal degeneration. Adv Exp Med Biol 2003; **533**: 13–8.

24. **Hong L, Zhang Y, Han S, Wang J, Pan Y, Liu N, Zhang X, Fan D.** Preparation and characterization of a novel monoclonal antibody specific to human ZNRD1 protein. Hybrid Hybridomics 2004; **23**: 65–8.

25. **Hong L, Zhang Y, Liu N, Liu C, Zhi M, Pan Y, Lan M, Sun L, Fan D.** Suppression of the cell proliferation in stomach cancer cells by the *ZNRD1* gene. Biochem Biophys Res Commun 2004; **321**: 611–6.

26. **Hong L, Han Y, Shi R, Shao X, Sun L, Fan D.** *ZNRD1* gene suppresses cell proliferation through cell cycle arrest in G1 phase. Cancer Biol Ther 2005; **4**: 61–5.

27. **Hinds PW.** A confederacy of kinases: Cdk2 and Cdk4 conspire to control embryonic cell proliferation. Mol Cell 2006; **22**: 432–3.

28. **Gegas VC, Doonan JH.** Expression of cell cycle genes in shoot apical meristems. Plant Mol Biol 2006; **60**: 947–61.

29. **Guardavaccaro D, Pagano M.** Stabilizers and destabilizers controlling cell cycle oscillators. Mol Cell 2006; **22**: 1–4.

30. **Nakayama KI, Nakayama K.** Ubiquitin ligases: cell-cycle control and cancer. Nat Rev Cancer 2006; **6**: 369–81.

31. **Davis T, Haughton MF, Jones CJ, Kipling D.** Prevention of accelerated cell aging in the Werner syndrome. Ann N Y Acad Sci 2006; **1067**: 243–7.

32. **Wang MS, Pan Y, Liu N, Guo C, Hong L, Fan D.** Overexpression of DARPP-32 in Colorectal Adenocarcinoma. Inter J Clin Prac 2005; **59**: 58–61.

33. **Clarke PA, Dickson JH, Harris JC, Grabowska A, Watson SA.** Gastrin enhances the angiogenic potential of endothelial cells via modulation of heparin-binding epidermal-like growth factor. Cancer Res 2006; **66**: 3504–12.

34. **Su JL, Yang PC, Shih JY.** The VEGF-C/Flt-4 axis promotes invasion and metastasis of cancer cells. Cancer Cell 2006; **9**: 209–23.

БЕЛОК, СОДЕРЖАЩИЙ ЦИНКСВЯЗЫВАЮЩИЙ ДОМЕН (*ZNRD1*): МОДУЛЯТОР МНОЖЕСТВЕННОЙ РЕЗИСТЕНТНОСТИ К ЛЕКАРСТВЕННЫМ СРЕДСТВАМ, ОНКОГЕНЕЗА И КЛЕТОЧНОГО ЦИКЛА

Ген *ZNRD1*, кодирующий белок с цинксвязывающим доменом, клонирован из HLA-A локуса. Показано, что ZNRD1 принимает участие в регуляции транскрипции и, возможно, в целом ряде биологических процессов, в том числе множественной устойчивости к лекарственным препаратам, онкогенезе и регуляции клеточного цикла. В обзоре обсуждены последние результаты в этой области и приведены данные о роли *ZNRD1* в процессах репарации ДНК.

***Ключевые слова*: ZNRD1, рак желудка, клеточный цикл, множественная устойчивость к лекарственным препаратам.**