WRAP53 is an independent prognostic factor in rectal cancer- a study of Swedish clinical trial of preoperative radiotherapy in rectal cancer patients

Hong Zhang1, Da-Wei Wang1,2, Gunnar Adell3 and Xiao-Feng Sun4*

Abstract

Background: Expression of WRAP53 protein has oncogenic properties and it is up regulated in several types of tumors.

Methods: We examined expression of WRAP53 protein in rectal cancers and analyzed its relationship to the response to preoperative radiotherapy and patient survival. The WRAP53 protein was examined by immunohistochemistry in normal mucosa, primary tumors and lymph node metastases from 143 rectal cancer patients participated in a Swedish clinical trial of preoperative radiotherapy.

Results: Frequency of WRAP53 protein expression was increased in primary rectal cancer compared to the normal mucosa (p < 0.05). In non-radiotherapy group positive WRAP53 in primary tumors (p = 0.03, RR, 3.73, 95% CI, 1.13-11.89) or metastases (p = 0.01, RR, 4.11, 95% CI, 1.25-13.14), was associated with poor prognosis independently of stages and differentiations. In radiotherapy group, positive WRAP53 in the metastasis correlated with better survival (p = 0.04). An interaction analysis showed that the correlations of WRAP53 with the prognostic significance with and without radiotherapy in the metastasis differed (p = 0.01). In the radiotherapy group, expression of WRAP53 in metastases gave a better outcome (p = 0.02, RR, 0.32, 95% CI, 0.13-0.84), and an interaction analysis showed significance between the two groups (p = 0.01).

Conclusion: WRAP53 may be a new biomarker used to predict prognosis and to select suitable patients for preoperative radiotherapy.

Keywords: WRAP53, Radiotherapy, Prognosis, Rectal cancer

Background

Colorectal cancer is one of the most common types of cancer worldwide [1], and 50% of the patients still develop local or distant recurrence, and eventually die from colorectal cancer despite surgery [2]. In order to improve outcome of the cancer patients, several approaches, such as radiotherapy and chemotherapy, have been introduced to the treatment of the cancer during the last decades. Preoperative radiotherapy has been proven to reduce local recurrence and further improve overall survival in rectal cancer patients [3-5]. However, there is marked difference in responses to the preoperative radiotherapy and prognosis between the cancer patients [6]. It is, therefore, a challenge to find valuable biomarkers for estimating different variations in the response to the preoperative radiotherapy and improving the patient prognosis.

WRAP53 gene (for WD40-encoding RNA antisense to p53) encodes a regulatory RNA essential for p53 function upon DNA damage [7]. WRAP53 also encodes a protein for maintenance of nuclear organelles called Cajal bodies [8-10]. WRAP53 protein has been found overexpressed in a broad range of human cancer cell lines in comparison to non-transformed cells. The WRAP53 overexpression promotes cellular transformation, whereas

© 2012 Zhang et al.; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
WRAP53 knockdown triggers apoptosis of cancer cells [11]. Common variations in WRAP53 (alias WDR79) have been associated with an increased risk for developing breast [12] and ovarian cancer [13]. However, there is no evidence concerning WRAP53 expression in rectal cancers, and its association with radiotherapy response.

In this study, we examined WRAP53 protein in biopsies, and surgical specimens from distant normal mucosa, adjacent normal mucosa, primary tumor and lymph node metastasis from the patients participated in a Swedish rectal cancer clinical trial of preoperative radiotherapy (Uppsala, 1986-11-17, Dnr. 86151) [4].

**Methods**

**Rectal cancer patients**

The sample profile of the rectal cancer patients showed in Figure 1. Biopsies (n = 98), distant normal mucosa (n = 118), adjacent normal mucosa (n = 81), primary tumors (n = 143) and lymph node metastases (n = 49) were from rectal cancer patients in the Southeast Swedish Health Care region, and they participated in the Swedish Rectal Cancer Clinical Trial of Preoperative Radiotherapy between 1987 and 1990, Radiotherapy, Uppsala, 1986-11-17, Dnr. 86151, [4]. There were 171 cancer patients who were randomised selected from Östergötland region, Sweden in the beginning. However, four patients were excluded due to surgically unresectable (advanced disease), and 24 patients had no available tissue specimen for this study. All patients had given their consent to participate in the study. The distant normal mucosa was histologically free from tumor taken from the distant margin, and 65 of them were matched with their primary tumors (i.e., from the same patients). Adjacent normal mucosa was adjacent to the primary tumor from the same tissue sections. Metastases were from the regional lymph nodes, and 37 of them were matched with their primary tumors. Seventy-eight of the patients received surgery alone and 65 received radiotherapy before surgery. The radiotherapy was given at a total of 25 Gy in 5 fractions before surgery over a median of 6 days (range, 5–12 days). Surgery was performed in a median of 3 days (range, 1–13 days) after radiotherapy. None of the patients received adjuvant chemotherapy before or after surgery, and all patients had locally resectable rectal adenocarcinoma. Mean age of the patients at diagnosis was 67 years (range, 36–86 years). All patients were followed-up, and the median of follow-up was 71 months (mean, 85 months). Other characteristics of the patients and tumors are present in Table 1.

The data for terminal deoxynucleotide transferase-mediated deoxyuridine triphosphate-biotin nick end-labeling (TUNEL) assay [14] and survivin expression by immunohistochemistry [15] were taken from previous studies performed in the same patients at our laboratory.

**Immunohistochemistry**

Tissue arrays sections (5-μm) were deparaffinized, rehydrated and cooked (0.01M Tris-EDTA, pH 9.0) for 5 minutes, incubated in peroxides block (Dako, Carpinteria, Rectal Cancer Patients (n=143)

![Figure 1 Profile of the rectal cancer patients including biopsies (taken before surgery and radiotherapy), and surgical samples of distant normal (DN), adjacent normal (AN), primary tumor (PT) and lymph node metastatic tumor (MT).](image)

**Table 1 Characteristics of patients and rectal cancers**

| Characteristics                        | Non-radiotherapy | Radiotherapy |
|----------------------------------------|------------------|--------------|
| No. | %   | No. | %   |
| --- | --- | --- | --- |
| Gender                                  |                  |              |
| Male                                     | 45              | 58           | 40             | 62           |
| Female                                   | 33              | 42           | 25             | 38           |
| Age (years)                             |                  |              |
| ≤ 67                                     | 33              | 42           | 26             | 40           |
| > 67                                     | 45              | 58           | 39             | 60           |
| TNM stage                               |                  |              |
| I                                           | 21              | 27           | 18             | 28           |
| IIA + IIA + IIB                          | 39              | 50           | 38             | 58           |
| IIIC + IV                                | 18              | 23           | 9              | 14           |
| Differentiation                          |                  |              |
| Well                                     | 5               | 6            | 4              | 6            |
| Moderately                               | 55              | 71           | 44             | 68           |
| Poorly                                   | 18              | 23           | 17             | 26           |
| Number of tumors                         |                  |              |
| Single                                   | 68              | 89           | 53             | 82           |
| Multiple*                                | 8               | 11           | 12             | 18           |
| Surgical type                            |                  |              |
| Rectal amputation                        | 42              | 54           | 25             | 38           |
| Anterior resection                       | 36              | 46           | 40             | 62           |
| Rectal margin                            |                  |              |
| Tumor free                               | 74              | 95           | 62             | 95           |
| Tumor involved margin                    | 4               | 5            | 3              | 5            |
| Distance to anal verge (cm)              |                  |              |
| Mean                                      | 7.3             | 8.6          |

*Other colorectal cancer or other type of tumor besides the present rectal cancer.
interaction methods.

tient survivals were further analyzed by multivariate and
alyzed by Cox
relationship between the WRAP53 and survival were
received radiotherapy. In the non-radiotherapy group,
who did not receive radiotherapy or the patients
sis in the lymph node (n = 49) to examine the expression
and localization of the WRAP53 protein. Figure 2 shows
expression of WRAP53 in rectal cancer and surrounding
cancers (n = 143), along with available distant (n = 118)
and adjacent (n = 81) normal mucosa as well as metasta-
sis in the lymph node (n = 49) to examine the expression
and localization of the WRAP53 protein. Figure 2 shows
expression of WRAP53 in rectal cancer and surrounding
tissue from the same patient. The WRAP53 protein was
localized both in the cytoplasm and the nucleus
Figure 2B, C).

In whole group of the patients, the WRAP53 expres-
sion was significantly increased from the distant
(p < 0.0001) or adjacent mucosa (p < 0.0001) to the pri-
mary tumor (Figure 2A, B, D). Thus, the WRAP53 is
overexpressed in primary rectal tumor compared to nor-
mucosa. However, the WRAP53 was not statistically
different between primary and metastatic tumor
(Figure 2D).

WRAP53 expression was further analyzed in patients
who did not receive radiotherapy or the patients
received radiotherapy. In the non-radiotherapy group,
WRAP53 expression was significantly increased from
the distant (p = 0.03) or adjacent mucosa (p = 0.03) to
the primary tumor (Figure 2E). The WRAP53 expression
was not statistically different between primary and meta-
static tumor (Figure 2E). A significant increase of the
WRAP53 was also found in primary tumors in the radio-
therapy group compared to distant normal mucosa
(p = 0.008) or adjacent normal mucosa (p = 0.01,
Figure 2F). There was no difference between the primary
tumor and metastasis in either of the groups (p > 0.05,
Figure 2E, F). Thus, the primary rectal tumors show
enhanced the WRAP53 expression compared to normal
mucosa independently of radiotherapy.

We observed an increased number of WRAP53 posi-
tive cases in the non-radiotherapy group (80% WRAP53
positive, Figure 2E) compared to the radiotherapy group
(69% WRAP53 positive, Figure 2F). To determine
whether WRAP53 expression was changed after the
radiotherapy, we analyzed the frequency of strong
WRAP53 expression in biopsies removed before radio-
therapy and in the corresponding primary tumors surgi-
cally removed after the radiotherapy. We found that
expression of WRAP53 protein was decreased after
radiotherapy: 45 biopsies (46%) expressed WRAP53
strongly compared to only 20 (31%) of primary tumors
after radiotherapy (p = 0.05, data not shown). Expression
of the WRAP53 was shown in the biopsy before radio-
therapy (Figure 2G) and in the corresponding primary
tumor after the radiotherapy (Figure 2H). There was no
such evidence in comparison of the biopsies with the
corresponding primary tumors without radiotherapy
(77% Vs. 69%, p = 0.30). This finding suggests that
expression of WRAP53 protein was down regulated in
rectal cancers upon radiotherapy.

Statistical analysis
The differences in the frequency of WRAP53 expression
and its association with clinicopathological/biological
factors were analyzed by McNemar’s or Chi Square. The
relationship between the WRAP53 and survival were
analyzed by Cox’s proportional hazard model. The pa-
tient survivals were further analyzed by multivariate and
interaction methods.

Results
WRAP53 Expression in rectal cancer
Immunohistochemistry was carried out in primary rectal
cancers (n = 143), along with available distant (n = 118)
and adjacent (n = 81) normal mucosa as well as metasta-
sis. The WRAP53 protein was localized in the lymph node
Figure 2B, C).

In whole group of the patients, the WRAP53 expres-
sion was significantly increased from the distant
(p < 0.0001) or adjacent mucosa (p < 0.0001) to the pri-
mary tumor (Figure 2A, B, D). Thus, the WRAP53 is
overexpressed in primary rectal tumor compared to nor-
mucosa. However, the WRAP53 was not statistically
different between primary and metastatic tumor
(Figure 2D).

WRAP53 expression was further analyzed in patients
who did not receive radiotherapy or the patients
received radiotherapy. In the non-radiotherapy group,
However, there was no significant correlation between WRAP53 in the primary tumor and survival in the radiotherapy (Figure 3E). Surprisingly, in the metastases with radiotherapy, positive WRAP53 turned out to have better prognosis (p = 0.04, Figure 3F) although its prognostic significance was lost in a multivariate analysis including both TNM stage and differentiation (p = 0.14). A multivariate interaction analysis showed that the correlations with prognostic significance of WRAP53 expression in the metastases without and with radiotherapy differed significantly (p = 0.01). Thus, positive WRAP53 expression is a marker of worse prognosis for the patients without radiotherapy. However, in the radiotherapy group, positive WRAP53 expression in the metastasis showed the opposite correlation to survival and was thus more favorable for those patients.

We further analyzed the impact of radiotherapy on the patients survival based on WRAP53 expression. In WRAP53 negative group of either primary or metastatic tumors, radiotherapy had no prognostic effect (p > 0.05, data not shown). In the WRAP53 positive group, radiotherapy did not play a prognostic role in primary tumors (p = 0.36, Figure 4A). However, radiotherapy did give a better prognosis in the metastasis in either univariate (p = 0.02, Figure 4B) or multivariate analysis including both TNM stage and differentiation (p = 0.02, RR, 0.32, 95% CI, 0.13-0.84). A multivariate interaction analysis showed that the correlations with prognostic significance of radiotherapy differed significantly between the patients having positive WRAP53 and the patients with negative WRAP53 in the metastasis (p = 0.01). Thus, WRAP53 may be a novel...
predictive marker for response to the radiotherapy in patients with metastatic rectal cancer.

We also analyzed whether WRAP53 was related to clinicopathological factors in both the non-radiotherapy and radiotherapy group. In the non-radiotherapy group, among 18 patients having local recurrence, 94% showed WRAP53 positive primary tumors, while in 60 non-local recurrences, 75% had WRAP53 positive primary tumors (p = 0.07). In the radiotherapy group, among 5 patients with non-distant recurrence, 100% showed WRAP53 positive expression, while in 16 patients with distant recurrence, only 56% had positive WRAP53 (p = 0.07).

**WRAP53 In relation to apoptosis in rectal cancer**

Based on the above results, especially the relationship of WRAP53 with radiotherapy and survival, we asked whether WRAP53 might function through an apoptotic pathway. We first analyzed whether WRAP53 was related to apoptosis and the survivin protein in the primary tumor samples (we had no available data of apoptosis and survivin expression from the lymph node metastasis).

In the radiotherapy group, the WRAP53 expression was positively related to apoptosis (p = 0.04) and negatively correlated to survivin (p = 0.002), namely, the tumors showing positive WRAP53 after radiotherapy, had a higher frequency of apoptosis and low frequency of surviving (data not shown). There was no such evidence in the non-radiotherapy (p > 0.05).

**Discussion**

To our knowledge, this is the first report concerning WRAP53 expression and its association with prognosis.
in rectal cancer. We found that WRAP53 was increased from normal mucosa to primary rectal cancers. Considering previous reports on oncogenic properties of WRAP53 overexpression of WRAP53 contributes to malignant transformation [11], the enhanced WRAP53 in rectal cancer may be a sign of its involvement in the conversion of normal mucosa into cancer. We did not find statistical difference in WRAP53 expression between primary tumors and metastases, suggesting that the WRAP53 plays such role in the early stage of tumor development (Figure 5A). This exposes WRAP53 as a potential "oncoprotein" in early development of rectal cancer, and a new biomarker for early diagnosis of rectal cancer.

The patient material investigated here is from a Swedish clinical trial of preoperative radiotherapy in rectal cancer patients [4]. Therefore, the 143 rectal cancer samples were divided into two groups; tumors not treated with radiotherapy (n = 78) and tumors treated with radiotherapy (n = 65) in order to analyze the role of WRAP53 in the two groups. In the primary tumors without radiotherapy, positive WRAP53 was related to a higher frequency of local recurrence, and worse survival independently of stage and differentiation. A similar result was shown in the lymph node metastases without radiotherapy. This finding strengthens the role of WRAP53 in rectal cancer and identifies WRAP53 as a poor prognostic marker of primary and metastatic tumors without radiotherapy. Surprisingly, in the metastases with radiotherapy, the opposite relationship was observed. Positive expression of WRAP53 protein in this group turned out to have a lower frequency of distant metastasis and better survival. An interaction analysis in the two groups of the metastases with or without radiotherapy showed that the prognostic value of WRAP53 differed significantly. This correlation was only observed in the metastasis and not the primary tumors with radiotherapy. Moreover, radiotherapy only prolonged the patients’ survival in the metastases expressing WRAP53 but not in the metastasis lacking WRAP53. Could the slightly lower WRAP53 levels in the metastases compared to primary tumors in combination with radiotherapy be of importance? The tumors positive for the WRAP53 are addicted to WRAP53 and die by apoptosis upon removal of WRAP53 [11]. Could radiotherapy of the metastasis reduce WRAP53 to a “critically low level", thus leading to induction of apoptosis? In such a case, it could explain why only the WRAP53 positive cells die upon radiotherapy, since they are addicted to WRAP53 expression. It could also explain why only the WRAP53 positive metastases die in response to radiotherapy, since they have less WRAP53 expression to start with and thus are more prone to reach a "critically low level" of WRAP53 required for induction of apoptosis (Figure 5B). Since primary tumors have a higher expression of WRAP53 protein the radiotherapy might not reduce the WRAP53 expression enough to induce WRAP53-specific apoptosis. It is well known that primary and metastatic tumors have different biological and clinical features. The numbers of genes distinguish metastases from primary tumors in colorectal cancer patients [16-19]. Even colon cancer cell lines, for example, KM12C, KM12SM and KM12L4a, with different metastatic potentials displayed different morphological and biological features after the treatments with radiation or drugs [20-22]. Thus, certain genes may be directly involved in primary tumor development whereas others play roles in metastasis. The weakness of this study is a small number of the patients in the each subgroup. It is necessary to confirm the results in a larger cohort of patients with rectal cancer with or without radiotherapy in the future. However, the results may raise a notion that we should not focus only on primary tumors but also on metastases in the identification of biomarkers when selecting patients for more efficient treatments.

The next question is whether the apoptosis pathway is involved in the association of WRAP53 with radiotherapy.
Inrectalcancerswithradiotherapy,therewasarelationshipofpositiveWRAP53withincreasedapoptosisanddecreasedsurvivin.Moreover,WRAP53positivecoloncancercellsunderwentspontaneousapoptosisuponreductionofWRAP53expression.WRAP53knockdownhasbeenreportedtoreultinaseignificantdecreaseinp53mRNAandsuppressionofp53inductionupondNA
damage.[7]Notably,thesurvivinexpressionisnegativelyregulatedbywild-typep53inthep53-dependentapoptoticpathway[23,24].Asmentionedpreviously,inthestrongexpressionofWRAP53inbiopsieswasreducedintheprimar
tumor after radiotherapy. This provides a possible mechanism to the effects of radiotherapy on cancer. The
curative effect of radiotherapy could partially be due to

inactivation/down-regulation of WRAP53 protein, subsequently leading to cells apoptosis and necrosis. Alterna
tively, the radiotherapy and WRAP53 might have an additive effect to cause cell death (Figure 5B). WRAP53 ex
dpression has been connected to prognosis and radiotherapy
in head-neck cancer [11]. In agreement with our study, high expression of WRAP53 was a marker for poor prog-
nosis in head-neck cancer. Furthermore, the high levels of WRAP53 were correlated to radio-resistance of the head-
neck cells. However, since no metastases of head-neck can-
cer were described it is difficult to compare our studies.

Conclusions
WRAP53 protein may be a potential “oncoprotein” in
rectal cancer development, and involved in induction of
apoptosis in response to radiotherapy. We propose
WRAP53 as biomarker for selecting suitable patients for
preoperative radiotherapy.

Competing interests
The authors declare that they have no competing interests.

Acknowledgements
This study was supported by grants from the Swedish Cancer Foundation,
Swedish Research Council and the Health Research Council in the South-East
of Sweden. The Authors thank Dr. David Hinselwood for linguistic revision.
Hong Zhang and Da-Wei Wang contributed equally to this work.

Author details
1Division of Biomedicine, The Systems Biology Research Center, University of
Skövde, Skövde, Sweden. 2Department of Stomatology, The Third Hospital of
Hebei Medical University, Hebei, China. 3Department of Oncology, Karolinska
University Hospital, Karolinska, Sweden. 4Division of Oncology, Department of
Clinical and Experimental Medicine, Faculty of Heath Science, Linköping
University, S-581 85, Linköping, Sweden.

Received: 23 January 2012 Accepted: 13 June 2012
Published: 17 July 2012

References
1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics 2010. CA Cancer J Clin 2010, 60:277–300.
2. Ross P, Heron J, Cunningham D. Cost of treating advanced colorectal
cancer: a retrospective comparison of treatment regimens. Eur J Cancer 1996, 32:13–17.
3. Hoffe SE, Shridhar R, Biagioli MC. Radiation therapy for rectal cancer:
current status and future directions. Cancer Control 2010, 17:25–34.
4. Swedish Rectal Cancer Trial. Improved survival with preoperative
radiotherapy in resectable rectal cancer. N Engl J Med 1997, 336:980–987.
5. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T,
Rutten HJ, Pahlman L, Glimelius B, van Krieken JHM, Leer JWH, van de
Velden CJH, the Dutch Colorectal Cancer Group: Preoperative radiotherapy
combined with total mesorectal excision for resectable rectal cancer. N
Engl J Med 2001, 345:638–646.
6. Myerson RJ, Michalski JM, King ML, Birnbaum E, Fleshman J, Fry R, Kodner I,
Lacey D, Lockett MA. Adjunct radiation therapy for rectal carcinoma:
Predictors of outcome. Int J Radiation Oncol Biol Phys 1995, 32:41–50.
7. Mahmoudi S, Henriksson S, Corcoran M, Méndez-Vidal C, Wiman KG,
Farnebo M. WRAP53, a natural p53 antisense transcript required for p53
induction upon DNA damage. Mol Cell 2009, 33:462–471.
8. Mahmoudi S, Henriksson S, Weltrech L, Smith S, Söderberg O, Strömblad S,
Wiman KG, Farnebo M. WRAP53 is Essential for Cajal Body Formation and
for Targeting the SMN Complex to Cajal Bodies. PLOS Biol 2010, 8:e1000521.
9. Kukoyi A, Steitz JA: A conserved WD40 protein binds the Cajal body
localization signal of scarRP particles. Mol Cell 2009, 34:47–57.
10. Venteicher AS, Abreu EB, Meng Z, McCann KE, Tems RM, Veenstra TD, Tems MP, Artand SE: A human telomerase holoenzyme protein required for Cajal body localization and telomere synthesis. Science 2009, 323:644–648.

11. Mahmoudi S, Henriksson S, Farnebo L, Roberg K, Farnebo M: WRAP53 promotes cancer cell survival and is a potential target for cancer therapy. Cell Death Dis 2011, 2:e1114.

12. García-Closas M, Kristensen V, Langner A, Qi Y, Yeager M, Roberg K, Farnebo M, Brinton L, Gerhard DS, Gram IT, Perou CM, Berensen-Dale A-L, Chanock S: Common genetic variation in TP53 and its flanking genes, WDR79 and ATP1B2, and susceptibility to breast cancer. Int J Cancer 2007, 121:2532–2538.

13. Schildkraut JM, Goode EL, Clyde MA, Iversen ES, Moorman PG, Berchuck A, Marks IR, Lissowska J, Brinton L, Peplonska B, Cunningham JM, Verkant RA, Rider DN, Chenevix-Trench G, Webb PM, Beesley JX, Phelan C, Sutphen R, Sellers TA, Pearce L, Wu AH, van den Berg D, Comrie D, Blund CK, Anderson R, Goodman MT, Lutjens CE, Thompson PJ, Gayther SA, Ramus SJ, Jacobs I, Kjaer SK, Hogdall E, Blaaker J, Hogdall C, Easton DF, Song H, Pharoah PO, Whittemore AS, McGuire V, Quaye L, Anton-Culver H, Ziegler A, Terry KL, Gramer OW, Hankinson SE, Tworoger SS, Calingaert B, Chanock S, Sherman M, García-Closas M, Australian Cancer Study (Ovarian Cancer), Australian Ovarian Cancer Study Group: Single nucleotide polymorphisms in the TP53 region and susceptibility to invasive epithelial ovarian cancer. Cancer Res 2009, 69:2349–2357.

14. Adell G, Zhang H, Evertsson S, Sun XF, Stål OH, Nordenskjöld BA: Apoptosis in rectal carcinoma: Prognosis and recurrence after preoperative radiotherapy. Cancer 2001, 91:1870–1875.

15. Knutsen A, Adell G, Sun XF: Survivin expression is an independent prognostic factor in rectal cancer patients with and without preoperative radiotherapy. Int J Radiat Oncol Biol Phys 2004, 60:149–155.

16. Koehler A, Bataille F, Schmid C, Ruemmele P, Waldeck A, Blaszyk H, Hartmann A, Hofstaedter F, Dietmaier W: Gene expression profiling of colorectal cancer and metastases divides tumours according to their clinicopathological stage. J Pathol 2004, 204:65–74.

17. Kleivi K, Lind GE, Diep CB, Meling GI, Brandal LT, Nesland JM, Myklebost O, Rognum TO, Giercksky KE, Skotheim RI, Lothe RA: Gene expression profiles of primary colorectal carcinomas, liver metastases, and carcinomatoses. Mol Cancer 2007, 6:doi:10.1186/1476-4598-6-2.

18. Koh KH, Rhee H, Kang HJ, Yang E, You KT, Lee H, Min BS, Kim NK, Nam SW, Kim H: Differential gene expression profiles of metastases in paired primary and metastatic colorectal carcinomas. Oncology 2008, 75:92–101.

19. Baffa R, Fassan M, Volinia S, O’Hara B, Liu CG, Palazzo JP, Gardiman M, Rugger M, Gomella LG, Croce CM, Rosenberg A: MicroRNA expression profiling of human metastatic cancers identifies cancer gene targets. J Pathol 2009, 219:214–221.

20. Yang L, Olsson B, Pfeifer D, Jönsson JL, Zhou ZG, Jiang X, Fredriksson BA, Zhang H, Sun XF: Knockdown of peroxisome proliferator-activated receptor β induces less differentiation and enhances cell-fibronectin adhesion of colon cancer cells. Oncogene 2010, 29:516–526.

21. Wallin Å, Ivarsson J, Holmblnd B, Ferread L, Sun XF: Anticancer effect of SN-38 on colon cancer cell lines with different metastatic potential. Oncol Rep 2008, 19:1493–1498.

22. Pfeifer D, Wallin Å, Holmblnd B, Sun XF: Protein expression following gamma-irradiation relevant to growth arrest and apoptosis in colon cancer cells. J Cancer Res Clin Oncol 2009, 135:1583–1592.

23. Hoffman WH, Biale S, Zilfitou JT, Chen J, Murphy M: Transcriptional repression of the anti-apoptotic survivin gene by wild type p53. J Biol Chem 2002, 277:2347–2357.

24. Mirza A, McGuire M, Hockenbery TN, Wu Q, Asar H, Black S, Wen SF, Wang L, Kirschmeier P, Bishop WR, Nielsen LL, Pickett CB, Liu S: Human survivin is negatively regulated by wild-type p53 and participate in p53-dependent apoptotic pathway. Oncogene 2002, 21:2613–2622.

Submit your next manuscript to BioMed Central and take full advantage of:

• Convenient online submission
• Thorough peer review
• No space constraints or color figure charges
• Immediate publication on acceptance
• Inclusion in PubMed, CAS, Scopus and Google Scholar
• Research which is freely available for redistribution

Cite this article as: Zhang et al. WRAP53 is an independent prognostic factor in rectal cancer- a study of Swedish clinical trial of preoperative radiotherapy in rectal cancer patients. BMC Cancer 2012 12:294.

doi:10.1186/1471-2407-12-294

Submit your manuscript at www.biomedcentral.com/submit