Tumor and Stem Cell Biology

Stress-Response Protein RBM3 Attenuates the Stem-like Properties of Prostate Cancer Cells by Interfering with CD44 Variant Splicing

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Abstract

Stress-response pathways play an important role in cancer. The cold-inducible RNA-binding protein RBM3 is upregulated in several types of cancer, including prostate cancer, but its pathogenic contributions are undetermined. RBM3 is expressed at low basal levels in human fetal prostate or in CD133+ prostate epithelial cells (PrEC), compared with the adult prostate or CD133−PrEC, and RBM3 is downregulated in cells cultured in soft agar or exposed to stress. Notably, RBM3 overexpression in prostate cancer cells attenuated their stem-cell-like properties in vitro as well as their tumorigenic potential in vivo. Interestingly, either overexpressing RBM3 or culturing cells at 32°C suppressed RNA splicing of the CD44 variant v8-v10 and increased expression of the standard CD44 (CD44s) isoform. Conversely, silencing RBM3 or culturing cells in soft agar (under conditions that enrich for stem-cell-like cells) increased the ratio of CD44v8-v10 to CD44s mRNA. Mechanistic investigations showed that elevating CD44v8-v10 interfered with MMP9-mediated cleavage of CD44s and suppressed expression of cyclin D1, whereas siRNA-mediated silencing of CD44v8-v10 impaired the ability of prostate cancer cells to form colonies in soft agar. Together, these findings suggested that RBM3 contributed to stem-cell-like character in prostate cancer by inhibiting CD44v8-v10 splicing. Our work uncovers a hitherto unappreciated role of RBM3 in linking stress-regulated RNA splicing to tumorigenesis, with potential prognostic and therapeutic implications in prostate cancer. Cancer Res; 73(13); 1–11. ©2013 AACR.

Introduction

It is now widely accepted that most tumors harbor cancer stem cells (CSC), which are crucial for their evolutionary capability. Consistent with such a function, CSCs display a greatly enhanced tumor-initiating capability and -sustaining capacity, a self-renewal potential, and the ability to spawn other subpopulations (1). Furthermore, CSCs have been proposed to play a critical role in the initiation of secondary tumors in metastatic sites and in the recurrence of tumors after therapy (2).

Despite the central role of the CSCs, however, their origin remains poorly understood, and it has been argued that, indeed, cancer cells may switch from a non-stem cancer cell (NSCC) to a CSC-like cell phenotype. For example, such phenotypic switching by cancer cells has recently been shown in melanoma where CSCs defined by the presence of CD133+ or JARID1B+ are not only able to regenerate the progeny with marker heterogeneity but could also arise from cells that did not express CD133 or JARID1B (3, 4). Thus, the unstable traits of CSCs may reflect the flexibility that favors tumor adaption to facilitate tumor progression. These data strongly suggest that epigenetic, rather than genetic, changes may drive phenotypic switching in cancer cells. Emerging evidence suggests that microenvironmental factors may be crucial for generating and maintaining the CSC subpopulation within tumors (5–7). For instance, the proinflammatory cytokine interleukin (IL)-6, which is a multifunctional chemokine in the tumor microenvironment, triggers the conversion of NSCCs into CSCs in breast and prostate cancer models (5). Similarly, hypoxia (6) and acidic stress (7) existing in the tumor microenvironment have been shown to be involved in maintaining and promoting the cancer stem cell-like phenotype in human glioma.

Temperature is another important element of the physical microenvironment that is capable of regulating cellular ‘stemness’ properties (8). For example, a precise and optimum temperature is essential for hatching of bird eggs, which, of course, are stem cells. Temperature effects are modulated at...
the cellular level by stress-response pathways that include heat-shock and cold-shock proteins (9, 10). In contrast to heat-shock proteins (HSP), which are induced by increased temperatures, cold-shock proteins (CSP) are induced by lowering the temperatures but are downregulated when temperatures are elevated (11, 12). The RNA-binding motif 3 (RBM3) is an evolutionarily conserved CSP (13) that has been shown to regulate the translation machinery and facilitate protein synthesis during hypothermic stress and in brain development, where it functions as an RNA chaperone to maintain RNA stability (14–18). In addition to its effect on protein synthesis, RBM3 has shown roles in enhancing cell proliferation (19), promoting erythropoietic differentiation (20, 21), and protecting cell death due to hypothermia or other stress conditions (22–24). In the present study, we show that RBM3 is related to a neural differentiation and that forced expression of RBM3 greatly attenuates the stem cell-like properties of the prostate cancer cells by inhibiting alternative splicing of exon v8-v10 of CD44.

Materials and Methods

Patients and samples

Primary prostate cancer samples (n = 79) and histologically normal prostate tissues (n = 20) were obtained from patients undergoing radical prostatectomy, from 1993 to 2007, at the Johns Hopkins Hospital. Patients with prostate cancer were followed up from 1 to 14 years (median, 2 years). Biochemical recurrence was defined as a postoperative elevation of serum PSA (0.2 ng/mL or greater) after radical prostatectomy (25). The endpoint of the follow-up in this study was the time to biochemical recurrence. Metastatic prostate cancer tissues were randomly divided into 4 groups, with 10 mice in each group. Then, 2 × 10^5 cells of the PC3-GFP clone #1, #2 and PC3-RBM3 clone #1, and #6 were separately inoculated into the mice in each group. Tumor growth was inspected and measured twice a week and the relative tumor volume was calculated.

Tumor xenograft in nude mice

Forty 6-week-old athymic nude mice (Harlan) were randomly divided into 4 groups, with 10 mice in each group. Then, 2 × 10^5 cells of the PC3-GFP clone #1, #2 and PC3-RBM3 clone #1, and #6 were separately inoculated into the mice in each group. Tumor growth was inspected and measured twice a week and the relative tumor volume was calculated.

PCR array and miRNA PCR array

The RT^2 Profile pathway-focused PCR array specific for human stem cell signaling and the miRNA PCR array specific for human cancers were purchased from SABiosciences. The complete gene lists for the PCR array and miRNA PCR array are available on the supplier’s website (http://www.sabiosciences.com/). PCR data was analyzed using Web-based software provided by the supplier. Fold-change was determined by comparing the gene expression of PCR-RBM3 clones with PC3-GFP clones.

PCR screening for CD44 mRNA splicing variants and sequencing

CD44 splice products were screened using a PCR-based method that was described previously (27). The primer sequences used for screening were described by the previous study (27). PCR products at the expected sizes were carefully extracted, purified, and directly sequenced on the Applied Biosystems 3730xl DNA Analyzer (Life Technologies).

ELISA assay

Soluble ectodomain of human standard CD44 was measured using the human CD44 ELISA kit (Abcam) according to the manufacturer’s instructions. Conditioned media from cell cultures were analyzed with a spectrophotometer at a wavelength of 450 nm.

Statistical analysis

Comparisons between 2 groups were made using the Student t test. Differences among more than 2 groups were analyzed by 1-way ANOVA test. Kaplan–Meier survival curves were used to evaluate the difference on tumor incidence among groups. The correlation coefficient (Pearson r) is used to assess the relationship between 2 data sets. Two-sided P values of less than 0.05 are considered significant.

For other details on materials and methods, see Supplementary Data.

Results

RBM3 expression is downregulated in prostatic stem cell-like cells

Although RBM3 mRNA is widely expressed in adult tissues (Supplementary Fig. S1A), its expression is significantly
decreased in the fetal testis and fetal prostate (Fig. 1A). To determine whether the lower levels of RBM3 in fetal tissues are related to the poorly differentiated but a more stem-like state of the fetal cells, CD133^+ cells and CD133^- cells from normal PrECs were separated by flow cytometry. In these primary cells, the CD133^- subpopulation has been shown to have stem-like features (26). As expected, RBM3 mRNA expression is extremely low in CD133^- cells in comparison with the CD133^+ subpopulation (Fig. 1B). In contrast, the expression of another CSP, namely cold-inducible RNA-binding protein (CIRBP), was found to be slightly increased rather than decreased in the same CD133^- cells, suggesting that the 2 CSPs may function differently (Supplementary Fig. S1B).

RBM3 mRNA was significantly increased in the primary prostate cancer samples in comparison with the normal prostate tissues. However, its expression was relatively decreased in the metastatic prostate cancer samples (Fig. 1C), suggesting a potential association between a decreased expression of RBM3 and cancer aggressiveness, which renders cancer cells more capable of metastasis. However, these findings do not preclude a role for RBM3 in the early events in prostate cancer where it is significantly upregulated. Further, immunohistochemical staining in the primary prostate cancer tissues showed that RBM3 was highly expressed in cancer lesions but not in the adjacent normal glands (Fig. 1D).

RBM3 overexpression attenuates the stem cell-like feature of PC3 cells

PC3 and DU145 cells were heated to 43°C or treated with paclitaxel, and then allowed to recover (28). RBM3 expression was found to be significantly lower in the surviving cells than the parental cells (Fig. 2A). In addition, it was determined that the expression of RBM3 in PC3 cells and DU145 cells that formed colonies in soft agar were significantly decreased as compared with their respective counterparts that were routinely grown in two-dimensional (2D) cultures (Fig. 2B). Considered together, these results suggest that a decrease of RBM3 expression is a more general response of cancer cells to stresses, including thermal, chemical, and recolonization stress. At the same time, this result also suggests that decreased RBM3 expression is compatible with an enhanced feature that favors cell survival in soft agar or after intensive cytotoxic stress that is commonly attributed to stem cell-like characteristics. In addition, PC3 cell clones overexpressing RBM3 (Supplementary Fig. S1C and S1D) showed a greatly attenuated capability to form colonies in soft agar (Fig. 2C and D) and to grow into prostaspheres from single cells when cultured without adhering to any physical surface compared with clones that were permanently transformed with the GFP control (PC3-GFP; Fig. 2E). Furthermore, PC3-RBM3 clones showed a significant reduction in tumor formation as compared with the PC3-GFP clones when cells were inoculated in nude mice. Thus, these data strongly suggest that enhanced...
expression of RBM3 significantly inhibit the stem cell-like phenotype of PC3 cells.

**RBM3 overexpression induces a cell differentiation trend and alters CD44 expression pattern in PC3 cells**

In order to determine the molecular mechanisms that may underlie the effects of RBM3 overexpression, the expression of a panel of stem cell-related genes in the 2 clones was examined. Among the genes with altered expression, 60% (6/10) of the genes that were significantly increased (P < 0.05) are related to cell differentiation, while more than 50% (5/9) of the decreased genes are associated with cell self-renewal (Fig. 3D; Supplementary Table S1). In addition to mRNA expression profiling, the expression of a panel of cell differentiation-related, in particular neural differentiation-related, miRNAs was found to be induced by RBM3 overexpression (Supplementary Fig. S2A). β3-tubulin, protein, which is a neuron-differentiation marker, was observed to be increased in the PC3 clones overexpressing RBM3 and co-expressed with RBM3 in the nerve fibers observed in human prostate tissue (Supplementary Fig. S2B and S2C). Taken together, these results suggest that overexpression of RBM3 in PC3 cells tends to induce neural differentiation.
CD44 mRNA levels were found to be decreased upon RBM3 expression in the PCR array assay as described earlier and this was confirmed by quantitative reverse transcription (RT)-PCR (Fig. 3E). In light of the intriguing relationship between CD44 expression and prostate CSC-like properties (29), CD44 protein expression was examined in the RBM3 overexpressing PC3 cells. Surprisingly, the standard CD44 protein that is approximately 85 kDa in molecular weight was not decreased but increased in PC3-RBM3 clones as compared with PC3-GFP clones. However, an intense band above 180 kDa was detected in the PC3-GFP clones but was extremely low in either of the 2 PC3-RBM3 clones (Fig. 3F). Further, CD44 tends to be clustered into foci at the edge of the cellular processes in PC3-RBM3 cells but not in PC3-GFP cells (Fig. 3G). This result suggests that, in addition to the expression level, the expression pattern of CD44 is also much altered following RBM3 overexpression in PC3 cells.

RBM3 inhibits splicing of the CD44 alternate exons v8–v10

CD44 proteins range in molecular weight from 85 to 230 kDa, presumably due to alternate splicing (29). Using the strategy established previously (Fig. 4A; refs. 27, 30), a band at a size of around 650 bp was found to be decreased in the 2 PC3-RBM3 clones compared with the control PC3-GFP clones when using c13 primer to amplify all of the potential variant exons (Fig. 4B). It was conjectured that the 650-bp product corresponds to a CD44 variant with inclusion of exon v8–v10, while the 270-bp product corresponds to the CD44 standard mRNA.
This speculation was subsequently verified by direct DNA sequencing (Supplementary Fig. S3A), and by siRNAs specific to CD44 variant exons v8–v10 (Fig. 4C and D and Supplementary Fig. S3B and S3C). These results suggest that the differential expression of the high-molecular-weight CD44 protein between PC3-GFP and PC3-RBM3 clones results from alternative splicing of the CD44 variant exons v8–v10. Indeed, by using the variant-specific primers (Supplementary Fig. S3B), it was confirmed that the expression of CD44v8-v10 was decreased and the expression of CD44s was increased in the PC3-RBM3 cells, compared with the PC3-GFP cells (Fig. 4E). On the other hand, decreasing the expression of RBM3 by specific siRNA in the PC3-RBM3 cells resulted in an increased expression of CD44v8-v10 but a decreased
expression of CD44s, which significantly increased the ratio of CD44v8-v10 to CD44s (Fig. 4E and Supplementary Fig. S3D). In contrast, when the expression of RBM3 in PC3 cells was induced under 32°C, the ratio of CD44v8-v10 to CD44s was decreased accordingly (Fig. 4G). Together, these results suggest that RBM3 inhibit splicing of CD44 variant v8-v10 while consequently increase the expression of its standard isofrom.

**CD44v8-v10 enhances CSC-like features by interfering with CD44 cleavage**

When splicing of CD44 v8-v10 was silenced by exon-specific siRNAs, the colony formation of the parental PC3 cells as well as the PC3-GFP clones in soft agar was significantly decreased (Fig. 5A). At the same time, the expression of CD44v8-v10 was found to be increased although the expression of CD44s decreased in the cell colonies that formed in soft agar as compared with the cells grown in 2D culture conditions (Fig. 5B). The same expression pattern of CD44v8-v10 and CD44s was observed in DU145 cells (Fig. 5C) as well, although they showed a significantly decreased ability to form colonies in soft agar as compared with PC3 cells (data not shown). Indeed, when the general primers that amplify all the variants of CD44 was used in a conventional RT-PCR, it was found that, in addition to the variant v8-v10, some other variants were also increased in the cell colonies that formed in soft agar for both PC3 and DU145 cells (Fig. 5D). These results indicate that the increase of CD44 variants is compatible with the capability of cancer cells to recolonize in soft agar, and suggest that RBM3 attenuates CSC-like features by, at least in part, inhibiting splicing of CD44.

It has been shown that CD44 undergoes sequential proteolytic cleavages by matrix metalloproteinases (MMP) including MMP9. This results in shedding of the ecto-CD44 that, in turn, regulates cell-extracellular matrix interaction, and release of the CD44 intracellular domain (CD44-ICD) that translocates to the nucleus and activates transcription of genes such as cyclin D1 (31, 32). Indeed, the expression pattern of cyclin D1 is consistent with that of CD44s in cell colonies that formed in soft agar or in cells cultured at 32°C, indicating a potential correlation between CD44s function and transcription of cyclin D1 (Supplementary Fig. S4A–S4C). Further, as shown in Fig. 5E and F, the addition of a MMP9 inhibitor significantly decreased the shedding of ecto-CD44 as well as the transcription of cyclin D1 in PC3-RBM3 cells but not in PC3-GFP cells (Fig. 5E and F). Given that the CD44v8-v10 is exclusively expressed in PC3-GFP cells, this result alludes to the possibility that CD44v8-v10 attenuates the cleavage of CD44 mediated by MMP9. In support of this conjecture, treatment with recombinant MMP9 significantly increased the expression of cyclin D1 in the LNCaP cells that overexpress CD44s alone but not in the cells that overexpress both CD44s and CD44v8-v10 (Fig. 5G and H and Supplementary Fig. S4D).

**CD44s is negatively related to the cancer stem-like features of prostate cancer**

To investigate further the significance of expressions of CD44s and CD44v in prostate cancer, the soft agar clonogenic assay was conducted in LNCaP cells, which lack endogenous expression of either CD44s or CD44v. Surprisingly, CD44s overexpression significantly inhibited the clonogenic capability of LNCaP cells, while coexpressing CD44v8-v10 with CD44s restored this capability (Fig. 6A). In support of this theory, the expression of CD44s was found to be decreased in metastatic prostate cancer as compared with localized tumors (Fig. 6B), and its expression was lower in the tumors of patients with recurrence than those without recurrence (Fig. 6C); however, the expression of CD44v8-v10 did not show any correlation with tumor progression (Supplementary Fig. S5), which may be attributed to the potential expression of other CD44 variants in tumor samples. Taken together, these data suggest that CD44s is negatively correlated with CSC-like features and, accordingly, with the progression of prostate cancer.

**Discussion**

Although accumulating evidence suggests that RBM3 plays an important role in multiple cellular processes during development and during stress response to a variety of stresses including hypothermia (11, 12), the role of RBM3 in cancer remains equivocal. For example, while RBM3 is thought to be a proto-oncogene that is upregulated in many cancers where it appears to protect cancer cells from mitotic catastrophe (19) or apoptosis (33), several studies also show that high RBM3 expression in cancer cells, especially in the nucleus, predicts a better prognosis in a variety of cancers, including prostate cancer (34–40). This negative correlation between RBM3 expression and tumor progression does not seem to support its oncogenic function but is in agreement with the present results showing decreased RBM3 expression in metastatic prostate cancer compared with primary cancer and, more importantly, that overexpression of RBM3 in PC3 cells greatly attenuates the stem cell-like feature of this aggressive cell line.

As a translation enhancer (18, 24), RBM3 expression may facilitate the high rate of cell proliferation and protein synthesis in early tumor development; however, it may not be required by or may even impede tumor progression, which needs several additional properties such as migration, invasion, and recolonization in the new microenvironment. This is evident by the present results showing that RBM3 expression drives differentiation and attenuates the stem cell-like features of highly aggressive cancer cells (PC3). In fact, disseminated tumor cells (DTC) that localize and take up residence in the bone marrow niche in prostate cancer are characterized by a nonproliferative status namely, quiescence or dormancy (41). Indeed, in the present study, the colonized cells in soft agar showed a dramatically decreased expression of cyclin D1 together with the decreased expression of RBM3, indicating a blocking of cell proliferation. It is speculated that the capability of slowing down to quiescence might be critical for survival and repopulation of tumor cells in a new microenvironment. Thus, it seems plausible that the upregulation of RBM3 is involved in the early development of prostate cancer, while its downregulation again is important for the subsequent steps in tumor progression.

As far as we are aware, this is the first report to show that RBM3 significantly inhibits splicing of the CD44v8-v10 variant.
Figure 5. CD44v8-v10 impairs standard CD44 (CD44s) function and enhances CSC-like features. A. Clonogenic assay in soft agar was conducted in parental PC3 cells and PC3-GFP clone after treatment with 2 different siRNAs specific to CD44v8-v10 (siC1 and siC2) or with non-target siRNA (siN). Values are mean ± SD (n = 3), *P < 0.05 in comparison to siN. B. Left, mRNA expression of CD44v8-v10 and CD44s was detected by qRT-PCR in PC3 cells when forming colonies in soft agar or growing routinely in 2D culture. Right, the mRNA levels of CD44v8-v10 relative to CD44s. Data are mean ± SD (n = 3), *P < 0.05. C. Same experiments as B in DU145 cells. Data are mean ± SD (n = 3), *P < 0.05. D. mRNA expressions of CD44s and CD44 variants were evaluated in the cells that formed colony in soft agar or that grew under regular 2D culture condition by a semi-nested PCR using the primers hs50, c13, and hs30. Arrows indicate the PCR products raised from CD44v8-v10; arrowheads indicate the PCR products raised from CD44s. M, molecular marker; N, negative control. E. G#2 and R#1 cells were treated with MMP9 inhibitor SB3CT or dimethyl sulfoxide (DMSO) for 24 hours, and soluble CD44 in culture media was detected by ELISA. Values are mean ± SD (n = 3), *P < 0.05. F. G#2 and R#1 cells were treated with MMP9 inhibitor SB3CT or DMSO for 24 hours, and mRNA expression of cyclin D1 was detected by qRT-PCR. Values are mean ± SD (n = 3), *P < 0.05. G. LNCaP cells were transfected with both pLenti-III-CD44s (pCD44s) and pLenti-III-CD44v8-v10 (pCD44v), or pCD44s alone, and then either treated with recombinant human MMP9 or remained untreated. The mRNA levels of cyclin D1 were detected by RT-PCR. Values are mean ± SD (n = 3), *P < 0.05. H. In the same experiment described in G, the protein levels of cyclin D1 were detected by Western blot. The intensity of Western bands was quantitatively evaluated as shown on the right. Actin was used as protein-loading control. Values are mean ± SD (n = 3), *P < 0.05.
in cancer. CD44 is commonly expressed as a wide variety of isoforms that mainly arise from alternatively spliced variants, which is particularly important for CD44 functions in tumor cells (42). Among the various isoforms, CD44v8-v10 has been reported to be the predominant form that is expressed in a variety of cancers (43–45). Indeed, overexpression of this isoform enhances bladder cancer progression potentially by decreasing the interaction of CD44 with hyaluronan (46). On the other hand, CD44s has shown an inhibitory role during cell quiescence in response to stress. TF, transcription factor; CD44-ICD, CD44 intracellular domain.

Figure 6. A, LNCaP cells were transfected with both pLenti-III-CD44s (pCD44s) and pLenti-III-CD44v8-v10 (pCD44v), or pCD44s alone, or empty vector (empty) for 48 hours. Cells were then subjected to clonogenic assay in soft agar for 4 weeks. Values are mean ± SD (n = 3); *P < 0.05. B, mRNA levels of CD44s were determined in human normal and prostate cancer tissues that are described in Fig. 1 by RT-PCR. C, mRNA levels of CD44s were compared between patients with recurrent prostate cancer (Rec, n = 44) and those without recurrent disease (Non-rec, n = 30). The experiment was repeated 3 times. Bars indicate mean ± SEM.

Figure 7. Proposed model for RBM3 regulation of CD44 variant splicing in cancer cells. RBM3, a stress-response protein, impairs the splicing of CD44v8-v10. When cells experience stress, RBM3 is downregulated. This results in the release of suppression of RBM3 of CD44 splicing, an increase CD44v8-10 expression, but a decrease in the expression of CD44s. In turn, CD44v8-v10 interferes with cleavage of CD44s and inhibits CD44-ICD-mediated cyclin D1 transcription, which may cause cell quiescence in response to stress. TF, transcription factor; CD44-ICD, CD44 intracellular domain.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Zeng et al.

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