Immunogenetics (2013) 65:315–332
DOI 10.1007/s00251-012-0677-2

REVIEW

miRNA and TMPRSS2-ERG do not mind their own business in prostate cancer cells

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Received: 5 August 2012 / Accepted: 25 December 2012 / Published online: 5 April 2013

Abstract Oncogenic fusion proteins belong to an important class that disrupts gene expression networks in a cell. Astonishingly, fusion-positive prostate cancer cells enable the multi-gene regulatory capability of miRNAs to remodel the signal transduction landscape, enhancing or antagonizing the transmission of information to downstream effectors. Accumulating evidence substantiates the fact that miRNAs translate into dose-dependent responsiveness of cells to signaling regulators in transmembrane protease serine 2: ETS-related gene (TMPRSS2-ERG)-positive cells. Wide ranging signaling proteins are the targets for the degree of quantitative fluctuations imposed by miRNAs. miRNA signatures are aberrantly expressed in fusion-positive cancer cells, suggesting that they have a cumulative effect on tumor aggressiveness. It seems attractive to note that TMPRSS2: ERG fusion has a stronger effect as tumors positive for the oncogenic TMPRSS2:ERG have dysregulated oncomirs and tumor suppressor miRNA signature. It is undeniable that a comprehensive analysis of the prostate cancer microRNAome is necessary to uncover novel microRNAs and pathways associated with prostate cancer. Moreover, the identification and validation of miRNA signature in TMPRSS2-ERG-positive prostate cancer cells may help to identify novel molecular targets and pathways for personalized therapy.

Keywords TMPRSS2-ERG · Prostate cancer · miRNA · Signaling · AR

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Introduction

Numerous recurrent chromosomal rearrangements are characterized and categorized in prostate cancer that are usually generated by the fusion of various 5′ regulatory elements to E twenty-six (ETS) transcription factors that results in an overexpression of these oncogenic transcription factors. Transmembrane protease serine 2:ETS-related gene (TMPRSS2:ERG), present in over 50 % of all prostate cancers, is the most commonly identified fusion gene (Kumar-Sinha et al. 2008). It is becoming progressively more understandable that the transcript abundances of miRNAs are subject to regulatory control by many more loci than previously observed for mRNA expression particularly in TMPRSS2-ERG-positive prostate cancer cells. Substantial fraction of information verifies the fact that miRNAs exist as highly connected hub–nodes and function as key sensors within the transcriptional network. There is an overwhelming list of high impact research that addresses miRNAs and fusion genes as independent determinants linked to prostate disease and progression. We provide an emerging landscape of the possible connection between miRNA regulation, prostate cancer, and TMPRSS2:ERG gene fusion status.

miRNAs in prostate cancer: oncomirs and tumor suppressors hold opposite ends of tug of war

miR-15a and miR-16-1 are tumor suppressors, which are homozygously deleted in a subset of prostate cancers (Porkka et al. 2011). These miRNAs are documented to target the oncogene BCL2, CCND1, and WNT3A. Introduction of miR-15a- and miR-16-specific antagomirs to normal mouse prostate results in marked hyperplasia, increased survival, proliferation, and invasiveness and enhances

tumor load in immunodeficient NOD-SCID mice (Bonci et al. 2008). miR-224 expression is notably downregulated in malignant prostate cancer (Mavridis et al. 2012). hsa-miR-141, hsa-miR-298, and hsa-miR-375 are upregulated in prostate tumors (Selth et al. 2012). Ten microRNAs (hsa-miR-16, hsa-miR-31, hsa-miR-125b, hsa-miR-145, hsa-miR-149, hsa-miR-181b, hsa-miR-184, hsa-miR-205, hsa-miR-221, hsa-miR-222) are downregulated and five miRNAs (hsa-miR-96, hsa-miR-182, hsa-miR-183, hsa-375) are upregulated (Schaefer et al. 2010).

miRNA expression in TMPRSS2-ERG-positive prostate cancer cells

From various studies, it seems that miRNAs may be sensing network states and responding to an entire network changes ranging from genesis of genomic rearrangements to miRNA regulation in fusion-positive cancer cells. We have just started to understand that miRNAs respond in a programmed manner to drive pathway changes via modulation of specific sets of mRNA. However, it is also reasonable to comprehend that regulation of targets by miRNAs is subject to various levels of control, and recent findings have presented a new paradigm: targets can reciprocally regulate the level and function of miRNAs. This mutual regulation of miRNAs and target genes is challenging our knowledge and interpretations of the gene-regulatory role of miRNAs in vivo. Mounting laboratory investigations have clarified the fact that miRNAs are frequently located in cancer-associated genomic regions and are often subject to rearrangements, breakpoints, loss of heterozygosity, and deletions.

It has recently been reported that genomic rearrangements result in loss of tumor suppressor subsets (Mao et al. 2011). The realization that the inappropriate production of individual miRNAs is strongly interconnected to genomic rearrangements has reinvigorated this particular research field (Jiang et al. 2012). In this review, we systematically put pieces of published cell-type-specific studies together to identify whether miRNA dysregulation acts as a trigger for genomic rearrangements or genomic rearrangements, consequently inducing aberrant miRNA expression, as this area is understudied and incompletely defined in prostate cancer.

Cell lines from thyroid adenomas with 19q13 rearrangement demonstrated robust expression of miRNAs of the C19MC cluster and the miR-371-73 cluster. Based on this appealing information, it might offer an exciting avenue that activation of miRNA subsets by chromosomal rearrangements might be not restricted to thyroid tumors (Rippe et al. 2010). It is prominent to note that the human locus for immunoglobulin genes encodes a miRNA. miR-650 gene existed in the exon 1 of λ light chain (IgLλ) and was found to be upregulated after an IgL rearrangement (Mraz et al. 2012). On a similar note, fusion gene AML1-ETO produced by the t(8;21) translocation facilitates heterochromatic silencing of pre-miR 223 in leukemic cells (Fazi et al. 2007).

Transient transfection of miR-138 in cells resulted in a significantly higher amount of chromosome breaks. Cells reconstituted for miR-138 displayed downregulated HR and reduced histone H2AX expression (Wang et al. 2011).

There is considerable experimental evidence that verifies the fact that a particular miRNA signature shows an underexpression after treatment in the TMPRSS2:ERG fusion-positive cases. Interestingly, among these, a subset of miRNAs contained an ERG-binding site and another subset lacked an androgen receptor (AR)-binding site. AR-binding site-deficient miRNAs are regulated through ERG in fusion-positive prostate cancer cells. Interestingly, miR-106a, miR-363, and miR-20b belong to the miR-106-363 cluster, which has been demonstrated to facilitate carcinogenesis. The ERG-binding sites are investigated to overlap with ARBSs. It is important to mention that approximately 90 % of AR-regulated genes are also ERG-regulated (Lehmusvaara et al. 2012). Recently, two separate distal regions upstream of the miR-221/222 promoter have been identified which are bound by the NF-kB subunit p65. In addition, a binding site for c-Jun was also identified that cooperated with that of p65 to trigger the expression of miR-221/222 (Galardi et al. 2011). miR-221 is downregulated in TMPRSS2:ERG-positive prostate cancer cells (Gordanpour et al. 2011). It is also intriguing to evaluate that overexpression of miR-221 or miR-222 in LNCaP or androgen-dependent cell line (LAPC-4) drastically repressed the level of the dihydrotestosterone (DHT)-induced upregulation of prostate specific antigen (PSA) expression and promoted androgen-independent growth of LNCaP cells. Using antagomirs against miR-221 and miR-222 recapitulated the responsiveness to the DHT induction of PSA transcription and simultaneously enhanced growth response of the LNCaP-Abl cells to the androgen treatment (Sun et al. 2009). Transfection of miR-221 and miR-222 into PC-3 cells caused a significant repression of ARHI expression. Genistein, a potential nontoxic chemopreventive agent, represses the expression of miR-221 and miR-222 (Chen et al. 2011a, b). The ectopic overexpression of miR-221 resulted in providing growth advantage to LNCaP-derived tumors in SCID mice (Mercatelli et al. 2008).

Androgen regulation of miR-32 and miR-148a has recently been confirmed by androgen stimulation of the LNCaP cells followed by expression analysis. It was additionally found that miR-32 and mir-148 expression was high in prostate cancer (Ferdin et al. 2010; Volinia et al. 2006; Murata et al. 2010; Jalaya et al. 2012), and it decreased after treatment with bicalutamide (Lehmusvaara et al. 2012). However, cells treated with goserelin displayed a higher expression of mir-148 (Lehmusvaara et al. 2012). The AR-binding sites in proximity

of these miRNAs were identified using the ChIP assay (Jalava et al. 2012).

miRNA and Notch signaling

The Notch pathway is often regarded as a developmental pathway, but components of Notch signaling are expressed and active in prostate carcinogenesis. With the advent of more sophisticated technologies, evidence has emerged that suggests tight correlation between miRNA and Notch signaling. Not surprisingly, Notch is a key regulator, but it is becoming increasingly clear that Notch signaling also has roles in the regulation of miRNA and interaction with AR. Understanding the many functions of Notch signaling in prostate carcinogenesis and its dysregulation is crucial to the development of new therapeutics that are centered around this pathway (Fig. 1).

Notch signaling initiates by attachment of Delta or Jagged ligand to the Notch receptor. After cleavage of the heterodimer Notch receptor (by ADAM and γ-secretase complex), a soluble fragment NICD is generated that is released into the cytoplasm. It shuttles into the nucleus, where it interacts with the IPT (immunoglobulin-like fold, plexins, and transcription factors)-domain-containing CBF1-suppressor of hairless-Lag1 (CSL) transcription factor (Fig. 1).

In the nucleus, binding of Notch proteins to CSL results in displacement of co-repressor proteins including silencing mediator of retinoic acid and thyroid hormone receptor (SMRT), SMRT/HDAC1-associated repressor protein, CBF1-interacting co-repressor 1, and various histone deacetylases (HDACs) from CSL. There is consequent recruitment of Ski-interacting protein, followed by co-activator proteins such as p300 and Mastermind-like 1, to the Notch–CSL complex, which promotes transcription of target genes that encode members of the HES, HEY, and Deltex families (Fig. 2).

Thus, Notch signaling controls key aspects of prostate cancer cell behavior and gene expression by modulating a network of miRNAs with cross-regulatory functions. The next paragraphs highlight the potential for complex interactions between coordinately regulated miRNAs within a network and how miRNA signatures control components of Notch-mediated signaling machinery.

Cells treated with anti-androgens bicalutamide and hydroxyflutamide demonstrated that a significant proportion of the AR was observed to remain in the nucleus in an inactive form. Receptor inhibition probably involved recruitment of co-repressor proteins (Notch effector Hey1), which interacted with antagonist-occupied receptor but inhibited AR-mediated transcription of target genes (Belandia et al. 2005; Powell et al. 2006). Yet another member of this family, HEYL, is a more potent repressor of AR activity (Lavery et al. 2011). miR-199b-5p is an important regulator of the Notch pathway through its targeting of the transcription factor HES1 (Garzia et al. 2009). Astonishingly, miR-199b-5p promoter region was characterized, which identified a Hes1-binding site. Therefore, enforced expression of Hes1 repressed the expression of miR-199b-5p (Andolfo et al. 2012) (Fig. 2). hsa-miR-199a-5p is downregulated in prostate cancer (Szczyrba et al. 2010). It has recently been identified that miR-524-5p acts as a tumor suppressor by negatively regulating Jagged-1 and Hes-1 (Chen et al. 2012).

Negative regulation of Notch signaling via miRNA

Based on the contemporary studies encompassing miRNA-mediated control of modulators of notch signaling, we provide a snapshot of how and at which steps miRNA antagonizes notch signaling by negatively regulating Notch, Jagged, and Maml. The Notch receptor in this pathway is extraordinary as most of its ligands are also transmembrane proteins. Therefore, signal transduction is restricted to neighboring cells. Even though the intracellular transduction of the Notch signal is surprisingly simple, with no secondary messengers, this pathway dysfunction is implicated in prostate cancer.

miR-34a and miR-34c target Notch1, Notch2, and Jag1. In addition, miR-34a targets c-Met mRNA (Bae et al. 2012; Yan et al. 2012; Du et al. 2007). miR-326 targets both the Notch-1 and Notch-2 3′-UTRs (Kefas et al. 2009). miR-449a and miR-449b are E2F1-inducible miRNA and target CDK6, Notch1, and Klf4 (Lize et al. 2010; Capuano et al. 2011) (Fig. 1). Ectopic expression of miR-34c resulted in inhibition of EMT other than its well-appraised features of negatively regulating mediators of Notch signaling (Yu et al. 2012a). miR-34a also targets Notch ligand delta-like 1 (Dll1) (de Antonellis et al. 2011). c-Myc and Notch-1 are regulated by let-7a and miR-144-dependent mechanisms, correspondingly (Sureban et al. 2011). miR-144 expression was reported to be decreased after treatment with bicalutamide (Lehmusvaara et al. 2012).

miR-206 and miR-150 target Notch3 (Song et al. 2009; Ghisi et al. 2011). miR-206 was found to be high in prostate cancer (reviewed by Ferdin et al. 2010). It is also interesting to note that miR-200 members target Notch pathway components, such as Jagged 1, Maml2, and Maml3, thereby repressing the expression of target genes (Brabletz et al. 2011). It is necessary to mention that the miR-200 family encompasses miR-200a, miR-200b, miR-200c, miR-141, and miR-429 and is repressed in prostate cancer. The miR-200 family is further characterized into subcategories: one codes for miR-200b, miR-200a, and miR-429 on chromosome 1 and the other codes for miR-200c and miR-141 located on chromosome 12 (Paone et al. 2011). It has recently been reported that treatment of prostate cancer cells with bicalutamide and

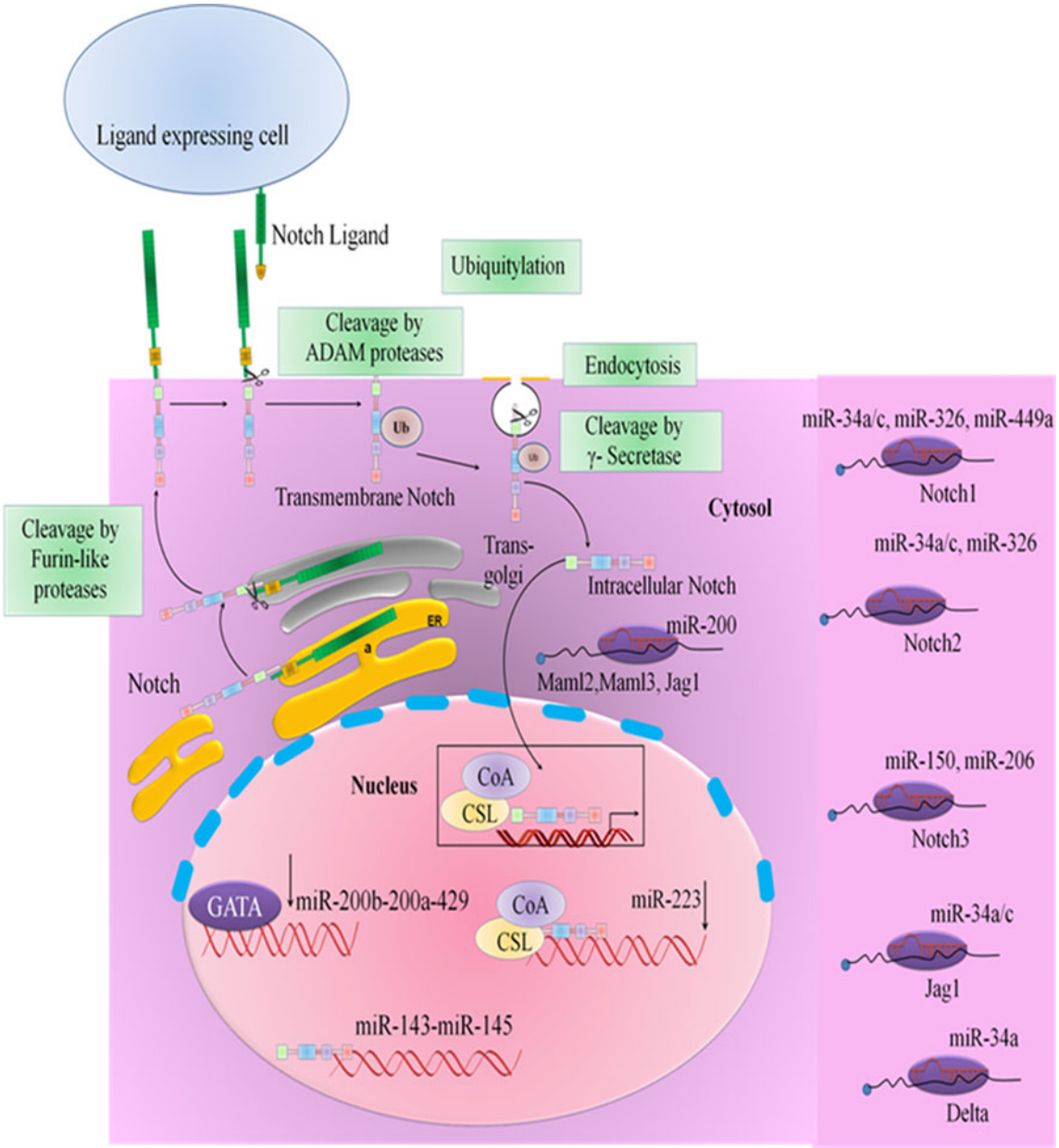

Fig. 1 Post-transcriptional processing of mediators of Notch signaling by miRNA

goserelin resulted in repression of miR-200a and miR-200b expression (Lehmusvaara et al. 2013). Using cell lines, it has been shown that hyperactivation of Notch-1 inhibits PTEN, which in turn results in Akt activation and p53 degradation via MDM2. Therefore, Notch signaling activation also represses p53-induced miR-122 expression (Manfe et al. 2012).

Positive regulation of Notch signaling via miRNA

There are pieces of information that provide strong evidence of miRNA regulation of negative signals within the Notch pathway and potentiating Notch signaling. In line with this concept, it has been shown that enforced expression of miR-34a results in suppression of a protein Numbl that antagonizes Notch-mediated signaling (Fineberg et al. 2012). Nemo-like kinase is a negative regulator of Notch signaling and is a target of miR-181 (Cichocki et al. 2011).

In NSCLC, it was found that Delta-tocotrienol induced the expression of mir-34a that restricted cell proliferation (Ji et al. 2012). Curcumin treatment extensively repressed miR-21 and miR-34a expression while stimulating the expression of let-7a miRNA (Subramaniam et al. 2012). miR-34a is significantly downregulated in human PCa, and transiently transfecting prostate cancer cells with miR-34a resulted in suppression of AR, PSA, and Notch-1 (Kashat et al. 2012).

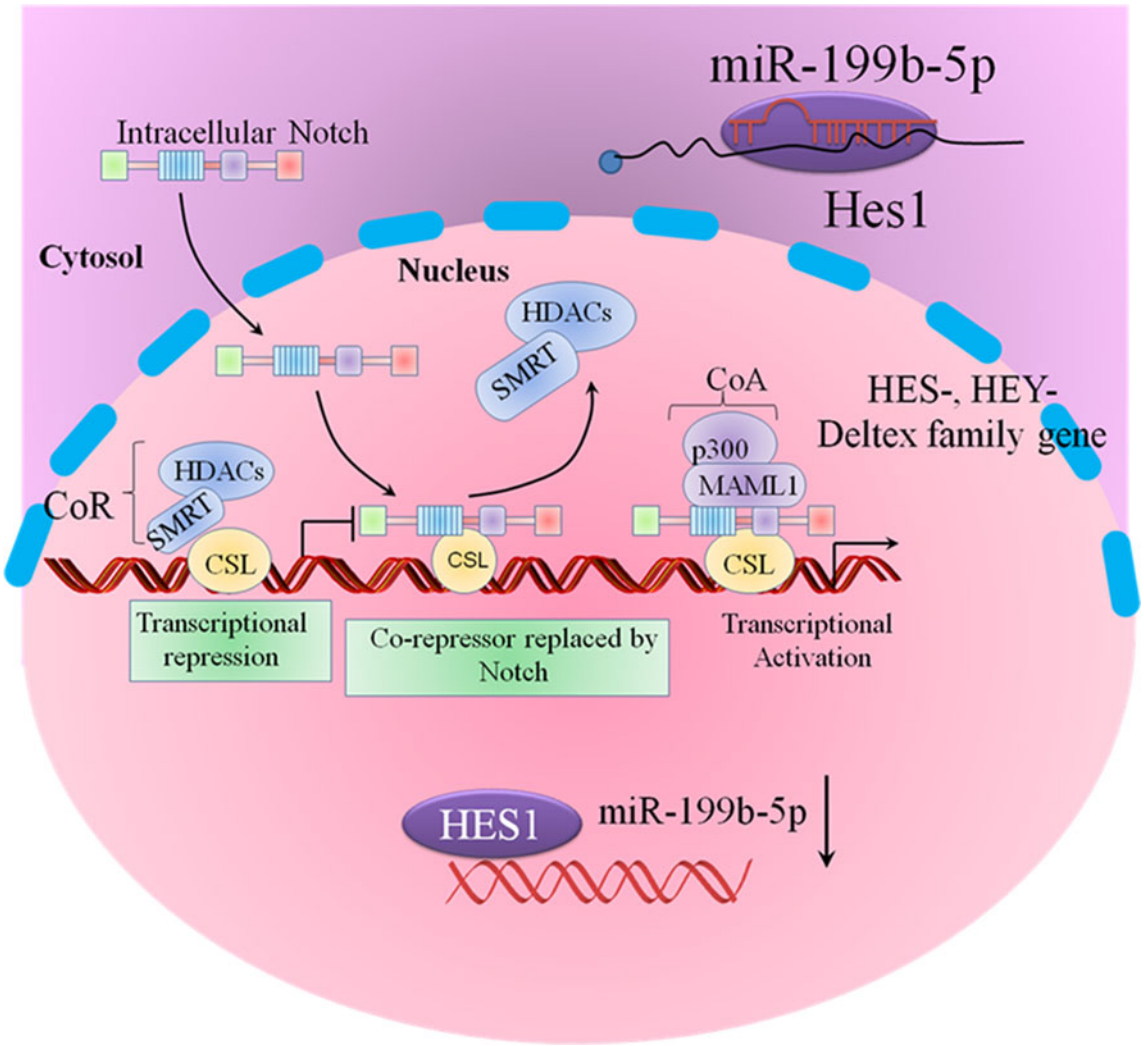

Fig. 2 Post-transcriptional processing of AID and TOP by miRNA. Expression of a set of miRNAs in oxidative stress

Notch signaling regulates the expression of miRNA

There is also circumstantial evidence that describes that various miRNA signatures are repressed as a consequence of Notch signaling. Notch signaling represses the expression of miR-223, and a simultaneous increase in expression of IGF1R is observed. However, using Notch signaling inhibitors, it was shown that there was an increase in miR-223 levels and a corresponding decline in the IGF1R as it was targeted by miR-223 (Gusscott et al. 2012). Expression of miR-223 was high in prostate cancer (reviewed by Ferdin et al. 2010). Jagged2 triggers repression of miR-200 via enhancing the binding of GATA-binding (Gata) factors to the promoter region of the miR-200b–200a–429 cluster (Yang et al. 2011). ChIP assays highlight the fact that the miR-143/145 cluster is a novel transcriptional target of Jagged-1/Notch signaling as Notch 1 intracellular domain-containing complexes bind to CBF1 sites in the miR-143/145 promoter (Boucher et al. 2011) (Fig. 1). miR-143/145 is downregulated in prostate cancer (Szczyrba et al. 2010). The emerging information on the subject of biology of miRNAs in the regulation of Notch signaling in prostate cancer is promising and may lead to a role(s) for these entities as diagnostic/prognostic markers and effective therapeutic tools for better molecularly targeted treatment of fusion-positive prostate cancer.

AID and TOP

It is worth describing that AID is expressed at a very low level in LNCaP cells; however, AR agonists and genotoxic stress both induced AID expression by ~3-fold and >60-fold, respectively. Likewise, the AID protein was exceedingly induced in IR-treated cells as early as 4 h (Lin et al. 2009). miR-155, miR-93, and miR-181b target AID mRNA. miR-93 expression was high in prostate cancer as reported by Volinia et al. (2006). miR-181 expression was low in prostate cancer (reviewed by

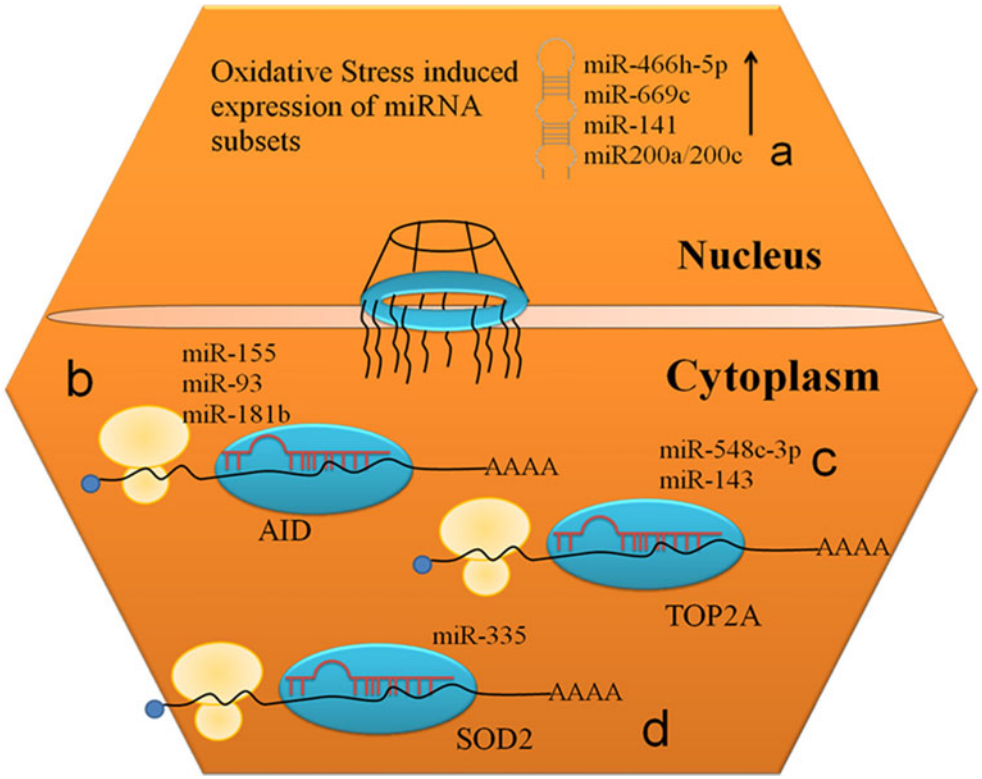

Fig. 3 Post-transcriptional processing of mediators of TGF, SHH, and Wnt signaling by miRNA

Ferdin et al. 2010) and miR-155 is documented to reduce potentially oncogenic translocations generated by AID (Borchert et al. 2011; de Yébenes et al. 2008; Dorsett et al. 2008) (Fig. 3).

It was tested in LNCaP cells that shRNA-mediated depletion of TOP2B impaired the activation of androgen-responsive genes. Furthermore, significantly reduced formation of biotin-labeled strand breaks was observed in TOP2B-depleted prostate cancer cells. Interestingly, pharmacological inhibition or RNAi-mediated depletion of TOP2B prior to DHT stimulation of cells resulted in complete reduction of de novo TMPRSS2-ERG fusion transcript genesis (Haffner et al. 2010). It is also evident that TOP2B and AR are highly co-expressed in luminal cells of prostate cancer precursor lesions. Several hints have appeared that indicate that TOP2A and TOP2B are negatively regulated by miRNA, and if there is an overexpression of TOP2A/TOP2B, it might be linked to dysregulation of miRNAs. This avenue has not been pursued in prostate cancer, but miRNA contributions to TOP2 isozyme regulation would be very interesting.

MiR-548c-3p negatively regulated TOP2A, and outstandingly, overexpressing miR-548c-3p selectively decreased DNA damage after treatment with chemotherapeutic agents (Srikantan et al. 2011). Nuclear factor-YB represses the expression of Top2α and is itself negatively regulated by miR-485-3p (Chen et al. 2011a, b, c). miR-143 and hsa-miR-139-5p also negatively regulate Top2α (Ugras et al. 2011; Miles et al. 2012). miR-139-5p is downregulated in prostate cancer (Fuse et al. 2012) and miR-23a negatively regulates TOP2B (Yu et al. 2010) (Fig. 3).

A recent publication further suggests that S-nitrosoglutathione induced TOP2-dependent DNA sequence rearrangements (Yang et al. 2013). Extra pieces of the puzzle that are needed are the identification of the responsible miRNA signatures that negatively regulate the expression of TOP2A and TOP2B in prostate cancer cells. Such a possibility can be tested experimentally on prostate cancer cell lines knock-down and/or knock-in assays. If, in addition, some of these dysregulations are associated with genomic rearrangements or with resistance to therapy, it opens up the possibility of patient-specific targeted therapy.

miRNA and oxidative stress

Research has provided verification that chromosome breaks observed in NHEJ-deficient mouse primary fibroblasts can be suppressed by growing the cells in reduced oxygen concentrations, which highlights the fact that oxidative metabolism is a major determinant of endogenous double-strand breaks in wild-type cells (Karanjawala et al. 2002). In a similar manner, several compounds have been documented to cause genomic instability. Superoxide-generating

herbicide paraquat gave rise to considerable chromosomal aberrations and sister chromatid exchanges in Chinese hamster fibroblasts (Nicotera et al. 1985). α-Pinene induces genome instability preferentially through mitotic alterations and DNA damage through reactive oxygen species (ROS) production (Catanzaro et al. 2012). In addition, loss of Tsa1, a peroxiredoxin, causes remarkably enhanced rates of mutations, chromosomal rearrangements, and recombination in *Saccharomyces cerevisiae* (Huang and Kolodner 2005). Later, another study indicated that loss of Tsa1 caused genome instability through constitutive activation of the DNA damage checkpoint and overproduction of intracellular dNTPs (Tang et al. 2009). Tsa1 worked synchronously with DNA repair and checkpoint mechanisms to protect *S. cerevisiae* cells against toxic levels of DNA damage (Iraqui et al. 2009). Cell studies using tsa1Deltatsa2Delta cells as a model indicated that these cells had increased hydrogen peroxide consumption. Additionally, these cells had remarkable conversion of ethanol to the 1-hydroxyethyl radical by SOD1 that resulted in increased DNA damage (Ogusucu et al. 2009).

There is also an evidence that indicates that anaerobic growth suppresses the gross chromosomal rearrangement rates in mutant yeast strains (Ragu 2007). Results suggest that hydrogen peroxide treatment upregulates the expression of endogenous L1 transcripts and simultaneous increase in γ-H2AX foci (Giorgi et al. 2011). It is of note that aged hematopoietic cells demonstrate enhanced in vitro chromosomal instability compared to that of young hematopoietic cells because of remarkably elevated oxidative stress in aged cells (Liu et al. 2012a). It has recently been explored that Rac2 GTPase alters mitochondrial membrane potential and electron flow through the mitochondrial respiratory chain complex III (MRC-cIII), thus producing substantial levels of ROS. MRC-cIII-generated ROS facilitate oxidative DNA damage to trigger genomic instability that consequently results in an accumulation of chromosomal aberrations (Nieborowska-Skorska et al. 2012).

In Prx1-rich LNCaP cells, multitargeted inhibition is more influential as evidenced by combinatorial inhibition of Prx1, and finasteride treatment produced a greater inhibitory effect on AR activity (Wu et al. 2011). Fascinatingly, Prx1 increases the binding of AR to DHT and decreases DHT dissociation rate and stabilizes the functional configuration of AR (Chhipa et al. 2009). Targeted inhibition of Prx2 reduced the expression of androgen-regulated genes (Shiota et al. 2011).

Oxidative stress induces an overexpression of Twist1 that in turn evokes robust expression of AR (Shiota et al. 2010). Therefore, oxidative stress and overexpressed AR might contribute to the genesis of genomic rearrangements. AR uses wide ranging co-activators (JunD) to stimulate the expression of oxidative stress-related genes (Mehraein-Ghomi et al. 2010).

There is increasing evidence that glucose deprivation-induced oxidative stress triggers the expression of miR-466 h-5p and miR-669c. This oxidative stress results in accumulation of ROS, compromised HDACs activity, and remarkably enhanced acetylation in the miR-466 h-5p promoter region (Druz et al. 2012). miR-141 and miR-200a are also documented to generate oxidative stress response (Mateescu et al. 2011).

let-7a and let-7b expression is downregulated in cells exposed to radiation (Saleh et al. 2011). Animal model studies indicated that reconstitution of Let-7c significantly reduced tumor burden in xenografts of human PCa cells (Nadiminty et al. 2012; Liu et al. 2012b).

It is worth describing that miR-335 and miR-34a inhibited expression of SOD2 and Txnrd2 by binding to the 3′-UTR of each gene, respectively (Bai et al. 2011). There are several studies which indicate that ROS mediates the expression of various miRNAs. In line with this approach, ROS induces miR-200c and other miR-200 family members (Magenta et al. 2011).

Correspondingly, metal sulfates were found to stimulate the expression of miRNA-125b and miRNA-146a (Pogue et al. 2011). Cells pretreated with ferric nitrilotriacetate (Fe-NTA)-induced oxidative stress displayed high miRNA-34a expression, and abrogation of miRNA-34a resulted in suppression of uncontrolled cellular proliferation (Dutta et al. 2007). Human embryo lung fibroblast cells were found to be transformed after exposure to arsenite and associated miR-21 overexpression (Ling et al. 2012). miR-128a increases ROS levels in medulloblastoma cells (Venkataraman et al. 2010). ROS stimulated the expression of miR-376b-5p in H9c2 (myoblast cell line) (Pan et al. 2012).

The above discussion and existing knowledge although indicate that cellular stresses are important triggers that induce genomic rearrangements. However, how these stresses especially oxidative stress modulate the expression of oncomirs and tumor suppressor miRNAs in prostate cancer remains largely unknown.

Androgen receptor crosstalk with different signaling pathways

It is now clear after a detailed investigation of the AR axis that AR is accompanied by modulators of the Wnt signaling pathway and has revealed new nodes for regulation, presenting the challenge of developing these strategies for optimal clinical gain and therein “outsmarting” the elusive adaptable AR.

In the absence of Wnt, Dishevelled protein remains cytosolic. In addition, destruction complex is active that degrades β-catenin. Wnt stimulation redirects Dvl recruitment to the plasma membrane by Frizzled receptors, which work

synchronously with LRP5–LRP6 co-receptors. Dvl polymers at the membrane act as a scaffold for Axin recruitment and subsequent inactivation. Wnt stimulation also results in phosphorylation of LRP5–LRP6 by CKI and GSK3. Phosphorylated LRP5–LRP6 couples with Axin, potentially providing an alternate mechanistic approach to recruit and inactivate Axin at the membrane (Fig. 4).

It has recently been described that TMPRSS2-ERG-positive prostate cancer cells displayed upregulated expression of Frizzled receptor 4 (FZD4) (Gupta et al. 2010). It had lately been found that ERG triggered the expression of WNT signaling genes: WNT11, WNT2, WNT9A, CCND1, and FZD7 (Mochmann et al. 2011). Literature provides us with ample information that Frizzled receptors are tightly regulated by miRNA clusters. FZD7 is negatively regulated by miR-23b (Zhang et al. 2011). miR-23b is downregulated in prostate cancer (Tong et al. 2009). However, its expression is enhanced after bicalutamide treatment (Lehmusvaara et al. 2012) (Fig. 4).

FZD4 is post-transcriptionally controlled by miR-493 (Ueno et al. 2012). FZD6 is a target of miR-194 (Krutzfeldt et al. 2012). miR-194 is upregulated in prostate cancer (Tong et al. 2009) and miR-31 negatively regulated the expression of FZD3 (Valastyan et al. 2009). It has recently been published that fusion-positive prostate cancer cells have downregulated frizzled receptors (FZD3,4,8) (Chow et al. 2012). However, the molecular detail that could teach us about the underlying mechanism of downregulation of Frizzled receptors is still unclear. Could it be because of enhanced degradation of frizzled receptors or miRNA-mediated post-transcriptional repression of frizzled receptors? Additionally, regarding whether or not frizzled receptors are acting as tumor suppressors, transient transfection assays could provide us with better and reasonable answers. It appears that miRNA-mediated regulation of Wnt signaling is a complicated mystery and it is vital to focus on various subsets of miRNAs which are aberrantly expressed and how Wnt signaling promotes genomic rearrangements.

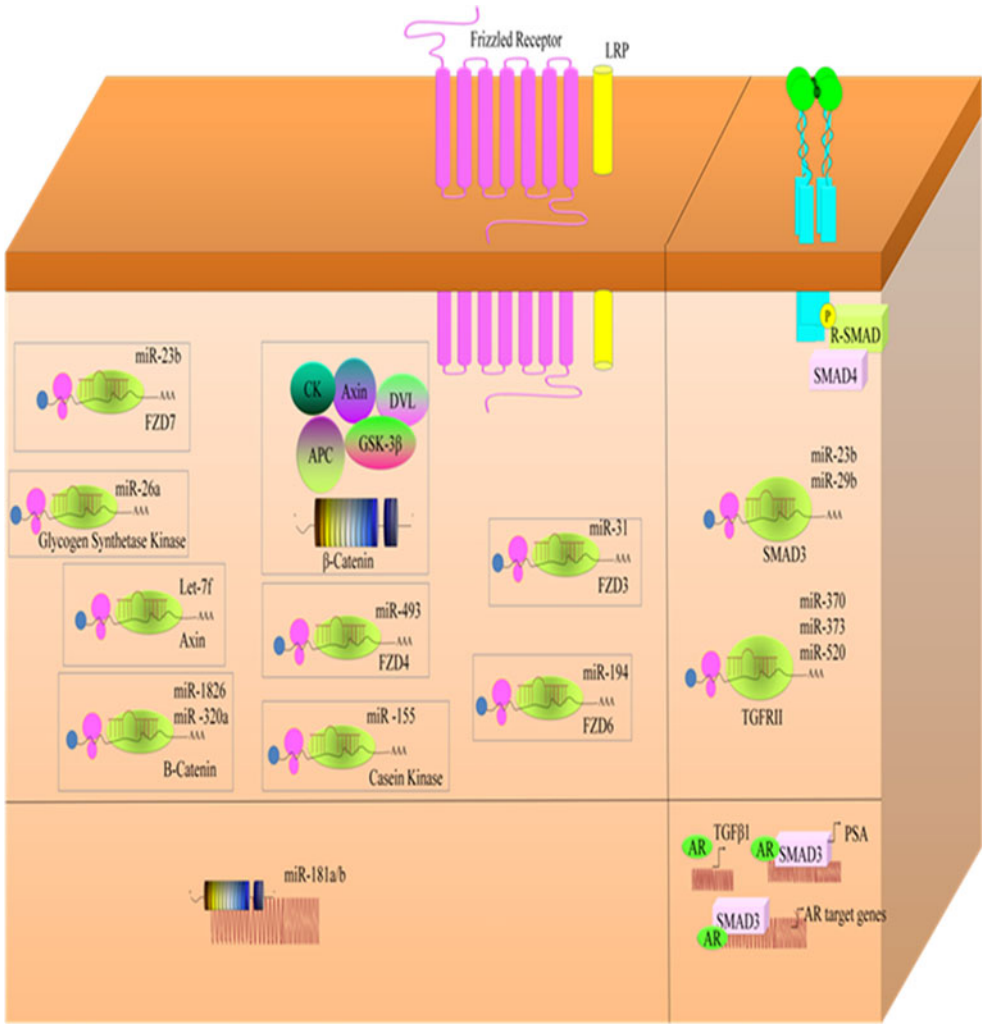

Fig. 4 Positive and negative regulation of target genes of Notch signaling

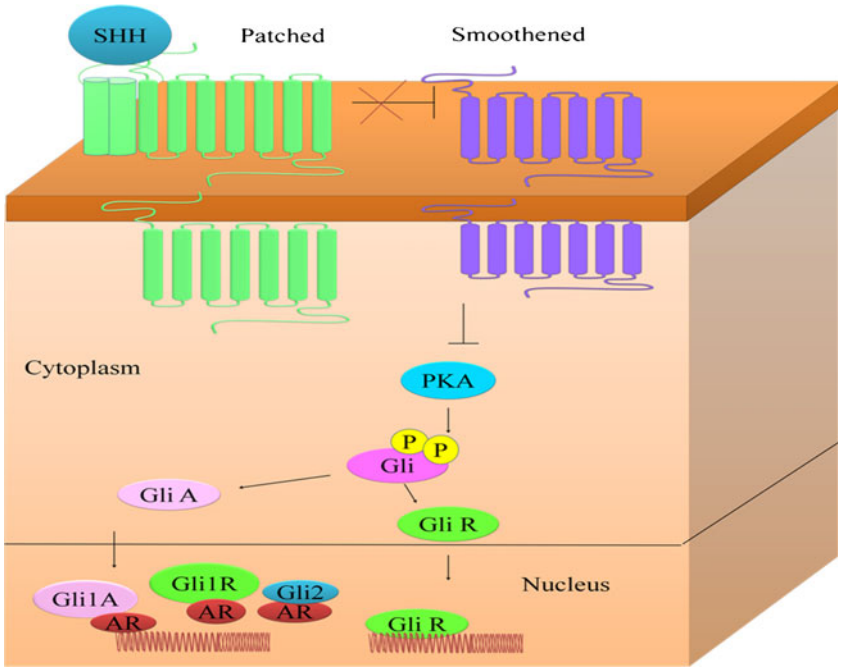

Fig. 5 In the figure, it has been shown that binding of SHH inhibits PTCH function and so releases smoothened (SMO) to protect GLI from cleavage. The Gli proteins are phosphorylated by protein kinase A (PKA), leading to their cleavage by the proteasome and the formation of carboxyl-terminus-truncated repressor (GliR); however, inhibition of PKA facilitates formation of Gli activator (GliA). In the nucleus, GliA and GliR promote and antagonize AR-mediated expression of target genes, respectively

Contradictory roles of Wnt5a

There are paradoxical findings on the topic of the role of Wnt5a in suppressing or promoting prostate cancer. It is worth mentioning that recombinant Wnt5a represses the invasive potential of 22Rv1 and DU145 cells, and inhibition of Wnt5a results in restoration of the invasive potential of 22Rv1 and LNCaP cells (Syed Khaja et al. 2012). Another study elaborated that Wnt5a repressed AR, and expression of Wnt5a and sFRP1 together did not lead to further inhibition of AR, signifying that sFRP1 and Wnt5a activate similar signaling pathway(s) to repress AR (Kawano et al. 2009).

Using high-throughput technologies and animal models for identification of the role of signalings in prostate carcinogenesis, several hints have emerged. In line with this approach, the impact of the T877A AR mutation on prostate tumor growth was tested in a known experimental prostate cancer model (TRAMP). Researchers provided confirmation that activity of the AR mutant in tumor growth was potentiated by cross-talk with modulators of signaling pathways. Wnt-5a, is a noncanonical Wnt ligand, is an activator for prostate tumors harboring the mutant AR. It was observed that Wnt-5a acted as an activator of AR-mediated prostate cancer growth. Targeted inhibition of Wnt-5a resulted in a considerable suppression of transactivation function of liganded AR (Takahashi et al. 2011).

Next, we discuss recent insights into post-transcriptional regulations of the Wnt signaling pathway and molecular interaction networks in the functions of AR and Wnt signaling pathway. These layers of regulation reveal how a simple signaling system can be co-opted to exert tactfully regulated, multipart responses.

Regulation of AR-mediated transcriptional network by the Wnt pathway

Using in vitro protein-binding assays, it was observed that inhibitor of β-catenin and T-cell factor (ICAT) retained the interaction between β-catenin and AR proteins. This complex triggered the expression of AR-specific target genes (Zhuo et al. 2011). However, it is also proved that sFRP1 reduces expression of the endogenous AR target genes PSA and Kallikrein 2, and astonishingly, repression of AR by sFRP1 does not involve Wnt/β-catenin signaling (Kawano et al. 2009). Inactivation of sFRP1 leads to uncontrolled AR activation that is a decisive step in prostate carcinogenesis.

It is a well-acclaimed fact that activation of Wnt/β-catenin signal transduction cascade in the mouse prostate results in an initial early increase in AR activity that synchronized with the early development of hyperplasia. However, it is significant to mention that with the development of PIN and HGPIN in this model, epithelial cell AR levels are gradually repressed. Initially, there is an increase in androgen-regulated target genes as observed in early stage prostatic hyperplasia and progressive suppression in HGPIN. In LPB-Tag/D.A. β-catenin mice, there is a context-dependent decline in the androgen receptor levels and in the androgen-regulated probasin promoter as seen by suppressed Tag levels. In discordance to the decreasing T-

antigen expression, Foxa2 is now expressed in LPB-Tag/D.A. β-catenin mouse prostate. Foxa2 is a target gene of Wnt signaling, and expression of Foxa2 indicates that Wnt/β-catenin signaling is active in these cells. It is intriguing to note a mutually exclusive expression pattern of large T-antigen and Foxa2, as detected by immunohistochemistry, that Tag (directed by AR signaling) is reduced in the cells that have activated Wnt/β-catenin signal transduction cascade. Intriguingly, there is a decline in AR protein content; however, AR mRNA increases in LPB-Tag/D.A. β-catenin prostate (Yu et al. 2011). It will be important to explore how Wnt signaling temporally regulates AR expression. Which proteins are utilized by the Wnt pathway to degrade AR? Whether the Wnt pathway co-opts the transforming growth factor (TGF) pathway and associated ubiquitin ligases to degrade AR protein or downstream effectors of Wnt pathway repress AR by recruiting co-repressor machinery at promoter region or use miRNA subsets to target AR is still a mystery that needs to be solved.

There is evidence that ectopic expression of Wnt-11 in LNCaP cells reduces the level of AR (Uysal-Onganer et al. 2010). There is substantial experimental verification that the WNT/β-catenin pathway triggers AR expression in prostate cancer cell lines by establishing an interaction with T-cell factor (TCF)/LEF-binding sites present in the promoter region of the AR. It is prominent to note that in discordance to the highly aggressive castration-resistant 22Rv1 cells which are able to drive a WNT-typical TCF-dependent reporter gene activity, LNCaP cells do not display activated β-catenin-dependent reporter gene expression. Therefore, it is understandable that targeted inhibition of the canonical WNT pathway using NO-releasing compound JS-K results in a concurrent decrease in AR and AR-V mRNA in 22Rv1 cells but not or to a lesser extent in LNCaP (Laschak et al. 2012). Likewise, some other findings are in concordance with the concept that high β-catenin nuclear localization and low or no AR expression is associated with a subpopulation of men with bone metastatic prostate cancer (Wan et al. 2012).

A recent finding indicates that HIF-1α and β-catenin coordinately enhance AR transactivation by stabilizing N–C interaction. Additionally, AR, HIF-1α, and β-catenin form a ternary complex on AREs (Mitani et al. 2012). There is emerging evidence that indicates that AR and β-catenin can be recruited to the promoter and enhancer regions of AR target gene PSA upon Wnt signaling (Schweizer et al. 2008).

miRNA and Wnt signaling

miR-26a targets GSK-3β that results in activation of β-catenin and induction of several downstream genes (Zhang et al. 2012a, b). miR-26 expression is high in prostate cancer (reviewed by Ferdin et al. 2010). miR-106b downregulates APC (Shen et al. 2013). miR-155 targets casein kinase-1α and enhances β-catenin signaling (Zhang et al. 2012c). Let-7f was upregulated in TIMP-1-depleted hMSCs and targeted axin 2, an antagonist of β-catenin stability (Egea et al. 2012). miR-1826 targets β-catenin and MEK1 (Hirata et al. 2012a, b). It is also interesting to note that overexpressing miR-221 and/or miR-222 resulted in elevated nuclear β-catenin levels (Rao et al. 2011). microRNA-181 expression is triggered upon activation of Wnt/β-catenin signaling. It is worth elaborating that seven putative β-catenin/Tcf4-binding sites are identified in the promoter region of the microRNA-181a-2 and microRNA-181b-2 transcripts (Ji et al. 2011) (Fig. 4). It is noteworthy that cells overexpressing miR-21 demonstrate high levels of β-catenin, TCF/LEF activity (Yu et al. 2012b). Overexpression of miR-516a-3p in highly metastatic derivatives (44As3 cells) resulted in suppression of nuclear β-catenin accumulation (Takei et al. 2012). miR-320a negatively regulates β-catenin and is downregulated in prostate cancer (Sun et al. 2012a; Szczyrba et al. 2010) (Fig. 4). However, discordantly, it was reported by another research group to be high in prostate cancer (reviewed by Ferdin et al. 2010). Overexpressing miR-122 in hepatoma cells remarkably downregulates the protein levels of Wnt1 and β-catenin (Xu et al. 2012). β-Catenin is negatively regulated by miR-214 and miR-548c-5p (Xia et al. 2012; Fang et al. 2012).

It is also investigated that by enhancing the degradation of β-catenin, prostate cancer can be repressed (Gwak et al. 2012). Silibinin inhibits the expression of LRP6 in prostate cancer cells, thus showing the inhibitory effect on Wnt/LRP6 signaling (Lu et al. 2012).

TGF and androgen receptor

Circumstantial evidence has improved remarkably our understanding related to the current patterns and paradigms in TGF signaling. It is now perceptible that TGF signals through TGFBR2 and ALK5 (also acknowledged as TGFBR1). Bone morphogenetic proteins (BMPs) signal via the BMP type II receptor (BMPR2) and ALK1, ALK2, ALK3, and ALK6.

In the presence of a ligand, receptor-based SMADs (R-SMADs) are activated by phosphorylation and heterodimerize with SMAD4. Active SMAD complexes enter the nucleus and accumulate there and trigger the expression of target genes. Cross-talk between AR and the TGF-β transduction pathway is well appraised. BMPs antagonize AR activity through Smad1, which functions as a co-repressor in prostate cancer cells (Qiu et al. 2007). In a similar manner, various other

Smads have documented interactions with AR. Smad3 interacts with AR, although there are contradictory findings on whether this enhances or represses AR activity (the following section describes in detail). However, it is understandable that downstream consequences of these hallmark interactions are highly context dependent, which might explain why androgen-regulated gene expression is stimulated by activin but inhibited by TGF-β1 (Fujii et al. 2004; Gerdes et al. 1998).

ERG is believed to suppress androgen signaling. As androgen deprivation potentiates TGF-β signaling in prostate cells, it is appealing to unravel how and at which steps ERG-mediated suppression of androgen signaling leads to an increase of TGF-β pathway utilization (Brase et al. 2011). Another study presented similar findings of ERG-induced TGF-β RII promoter activity (Im et al. 2000). It would be interesting to test if AR and TGF signaling antagonize each other using exclusive miRNA clusters. It would additionally be valuable to note whether or not subsets of miRNA are triggered characteristically by either AR or TGF and lose their expression if respective signaling is nonfunctional.

Diametrically opposed interactions of SMAD3 with AR

It is a well-established fact that LNCaP cells treated with DHT displayed an increase in PSA mRNA expression; however, astonishingly, addition of Smad3 further enhanced DHT-induced PSA expression. Co-expression of Smad3 and Smad4 reversed the Smad3-enhanced PSA mRNA expression (Kang et al. 2002). Similarly, activin A triggered AR gene transcription through Smads through binding to AR promoter as targeted inhibition of Smad3 by siRNA decreased activin A-promoted AR expression (Kang et al. 2009). Contrarily, using transient transfection systems, it was convincingly revealed that Smad3 specifically repressed transcriptional activation mediated by AR on two natural androgen-responsive promoters (Hayes et al. 2001). Smad3 is a target of miR-23b and miR-29b, and astonishingly (Fig. 4), miR-23b/-27b is downregulated in prostate cancer (Leone et al. 2012; Sun et al. 2012b).

miRNA-mediated regulation of TGF receptors

As discussed previously, upon ligand binding, TGFβ-RII phosphorylates and activates TGFβ-RI, which initiates the downstream signaling by phosphorylating the R-Smads. On a similar note, it is worth highlighting that considerably increased AR expression is detectable in TRAMP mice with inactivated DNTGFβRII, compared with TRAMP mice with wild-type TGFβ-RII (Pu et al. 2009). Reporter assays confirmed 3′-UTR of TGFβ-RII as target of miR-370, and enforced expression of miR-370 resulted in a decrease in TGFβ-RII expression and reduced Smad3 phosphorylation (Lo et al. 2012). miR-370 is upregulated in prostate cancer (Wu et al. 2012). However, another research group reported a low expression of miR-370 in prostate cancer (Lehmusvaara et al. 2012). Likewise, in MDA-MB-231 cells, miR-520/373 downregulated the expression of TGFβ-RII (Keklikoglou et al. 2011). miR-520/373 are downregulated in prostate cancer (Yang et al. 2009) (Fig. 4). However, its relationship with TGFβ-RII needs to be investigated in prostate cancer cells. TGFβR2 is a direct target of miR-21 and miR-590-5p (Yu et al. 2012b; Jiang et al. 2012; Kim et al. 2009). miR-21 expression is high in prostate cancer (reviewed by Ferdin et al. 2010).

AR-mediated regulation of regulators of TGF signaling

Mounting evidence verified the fact that ligand-bound AR inhibited TGF-beta transcriptional responses through repressing the binding of Smad3 to Smad-binding element (Chipuk et al. 2002). ChIP assays underscored the fact that there was androgen-dependent recruitment of AR to the ARE-containing regions of the TGF-beta1 gene. In addition to the positive regulation of TGF, a negative ARE was detected in the TGF-beta1 promoter that signified the fact that both positive and negative AREs existed in the androgen-regulated transcription of the TGF-beta1 promoter (Qi et al. 2008). It has recently been investigated that heterozygosity of the Hexim-1 gene in the prostate cancer mice model and the TRAMP-C2 cell line results in Cdk9-mediated serine phosphorylation on proteins such as the AR and the TGF-β-dependent downstream signaling mediators (Mascareno et al. 2012).

Apparently, there are contradictory findings regarding the relationship of SMAD3 with AR in stimulating or repressing the transcriptional network. It remains to be seen how SMAD3 contributes to the genesis of genomic rearrangements in prostate cancer. Another possibility is that AR and SMAD3 work synchronously to trigger genomic rearrangements and later "rearranged cells" opt different mechanistic approaches to repress AR signaling via repressing AR at the transcriptional and post-transcriptional levels. It is also previously added that fusion-positive prostate cancer cells have inactive AR signaling that is counterbalanced by TGF signaling. Future research must be focused on the miRNA signatures that regulate SMAD activity to evoke or antagonize context-dependent transcriptional programs in a prostate cancer cell. An equally important challenge is a better understanding of the functional role of signal strength and duration in prostate cancer cells that work with AR to trigger the expression of target genes and genomic rearrangements.

miRNA SHH

The absence of Hh leads to repression of Smo by the transmembrane receptor Ptch; concurrently, Gli1/2 are phosphorylated and are degraded by proteosome. On the contrary, binding of Hh to Ptch results in activation of Smo. Resultantly, Gli1/2 are released from the Smo protein complex and move into the nucleus and trigger expression of Hh-associated genes. There is emerging evidence that highlights the regulation of mediators of hedgehog signaling by miRNA and expression of miRNA by Hh signaling.

SHH is contributory to prostate carcinogenesis (Sanchez et al. 2004). More interestingly, it was observed that SHH expression was found to be downregulated by DHT in all AR-positive cells. Proof of the concept was further provided treating cells with bicalutamide that resulted in an enhanced expression of SHH. Hh pathway inhibitor, cyclopamine-inhibited AR activity and prostate cancer cells co-treated with bicalutamide and cyclopamine displayed restoration of expression of GLI and PTCH (Sirab et al. 2012). However, there is a direct piece of evidence that indicates that SHH signaling antagonizes AR-mediated transactivation via Gli1 that acts as a co-repressor and associates with AR (Chen et al. 2011c) (Fig. 5). Contrary to the previously discussed role of Gli proteins, there is a finding that suggests that overexpression of Gli1 or Gli2 in LNCaP cells enhances AR-specific gene expression in the absence of androgen. Furthermore, the AR protein was co-immunoprecipitated with Gli2 protein from transfected 293 T cell lysates (Chen et al. 2010). There is a clue that indicates that miR-324-5p targets and functionally suppresses Gli1; however, its expression and correlation with Gli proteins needs to be tested in prostate cancer (Ferretti et al. 2008). Although there is a finding that indicates that miR-324-5p is downregulated in prostate cancer (Fuse et al. 2012), it needs to be further explored in fusion-positive prostate cancer cells.

Concerted microRNA control of Hedgehog signaling in prostate cancer cells

Shh signaling represses the expression of miR-206 (Radzikinas et al. 2011). miRNA-206 overexpression is documented to inhibit ERα expression (Chen et al. 2012). Stable miR-302-367 cluster expression targets CXCR4 pathway and inhibition of CXCR4 leads to the impairment of the SHH-GLI-NANOG network (Fareh et al. 2012). The miR-17/92 cluster expression is triggered by Shh via signaling mediator N-myc (Northcott et al. 2009).

Conclusion

The last decade has witnessed extraordinary developments in the genetic and epigenetic analyses of solid tumors. Transcriptional and DNA copy-number studies have outstandingly enhanced our knowledge and characterization of solid tumors and highlighted the pattern of genomic aberrations associated with outcome. AR signaling involves translocation of AR into the nucleus to stimulate the expression of its target genes. AR is accompanied by wide ranging end step modulators of various signaling cascades that act as co-activators and concomitantly trigger the expression of AR-associated gene network. Certain hints have appeared that suggest that AR signaling is potentiated by transduction pathways and these pathways contribute to the genesis of genomic rearrangements. Furthermore, there is a complicated web that connects signaling pathways and miRNA clusters. Miscellaneous cellular stresses induce multiple transduction cascades. The identification of altered transcriptional and translational silencing by microRNAs shows a layer of additional intricacy to the regulation of gene expression in prostate cancer. The advent of massive parallel sequencing has allowed whole cancer genomes to be sequenced with extraordinary speed and accuracy providing insight into the bewildering complexity of gene mutations present in prostate cancer.

This is also worth indicating that there are knowledge gaps despite partitioned research and unconfirmed data, and in some cases, even conflicting results witness the need for a deeper insight into the multifaceted mechanisms that underpin miRNA dysregulation in fusion-positive prostate cancer cells. It is noteworthy that miR-29a and miR-1256 are downregulated in prostate cancer and treatment of cells with isoflavone demethylates the methylation sites in the promoter sequence of miR-29a and miR-1256, resulting in an upregulation of miR-29a and miR-1256 expression (Li et al. 2012). A recent report identified 47 long-range epigenetic silencing regions in prostate cancer, spanning about 2 Mb and harboring about 12 genes, with frequently occurring tumor suppressor and miRNA genes (Coolen et al. 2010). Furthermore, a current finding provides information that miR-205, miR-21, and miR-196b are epigenetically repressed, and miR-615 epigenetically activated in prostate cancer cells (Hulf et al. 2011). However, it needs to be determined in fusion-positive prostate cancer cells. It is also important to mention that epigenetics of fusion-positive and fusion-negative prostate cancer cells might differ.

Identification of an increased complicated web of oncogenic and tumor suppressor miRNA and epigenetics needs to be investigated in a context-dependent manner. Although there are advancements in the identification of DNA hyper- and hypomethylated miRNAs, these are not unveiling the relationship of the regulation of signaling cascades that synergizes with AR. A recent study gives a clue that SNPs

within miRNA influence the expression of mature miRNA in a cell-type-specific manner (Kim et al. 2012). It additionally needs to be tested in fusion-positive prostate cancer cells.

Therefore, while there is considerable knowledge concerning the genes that are mutated in prostate cancer, however, the number of pathways through which they function in fusion-positive prostate cancer cells is relatively small. Future studies must provide a compelling focus for pathway-directed, rather than traditional tumor-type-specific interventions.

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