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Infection, Genetics and Evolution 88 (2021) 104669

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Review

Covid-19 pathogenesis in prostatic cancer and TMPRSS2-ERG regulatory genetic pathway

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ARTICLE INFO

Keywords:
TMPRSS2-ERG
Prostate
Cancer
SARS-CoV-2
Fusion

ABSTRACT

Members of Coronaviridae family have been the source of respiratory illnesses. The outbreak of SARS-CoV-2 that produced a severe lung disease in afflicted patients in China and other countries was the reason for the incredible attention paid toward this viral infection. It is known that SARS-CoV-2 is dependent on TMPRSS2 activity for entrance and subsequent infection of the host cells and TMPRSS2 is a host cell molecule that is important for the spread of viruses such as coronaviruses.

Different factors can increase the risk of prostate cancer, including older age, a family history of the disease. Androgen receptor (AR) initiates a transcriptional cascade which plays a serious role in both normal and malignant prostate tissues. TMPRSS2 protein is highly expressed in prostate secretory epithelial cells, and its expression is dependent on androgen signals. One of the molecular signs of prostate cancer is TMPRSS2-ERG gene fusion. In TMPRSS2-ERG-positive prostate cancers different patterns of changed gene expression can be detected. The possible molecular relation between fusion positive prostate cancer patients and the increased risk of lethal respiratory viral infections especially SARS-CoV-2 can candidate TMPRSS2 as an attractive drug target. The studies show that some molecules such as nicotinamide, PARP1, ETS and IL-1R can be studied deeper in order to control SARS-CoV-2 infection especially in prostate cancer patients.

This review attempts to investigate the possible relation between the gene expression pattern that is produced through TMPRSS2-ERG fusion positive prostate cancer and the possible influence of these fluctuations on the pathogenesis and development of viral infections such as SARS-CoV-2.

List of abbreviations

SARS-CoV	severe acute respiratory syndrome coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus
SARS-CoV-2	SARS-coronavirus 2
PCa	Prostate cancer
TMPRSS2: ERG	transmembrane protease serine 2:vets erythroblastosis virus E26 oncogene homolog
AR	Androgen receptor
DHT	metabolite 5-dihydrotestosterone
AREs	androgen response elements
S	spike protein
ACE2	angiotensin-converting enzyme 2

1. Background

Coronaviridae family has several members that constantly circulate in the human population and are usually the source of mild respiratory illnesses (Corman et al., 2019). Conversely, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) are two members of this family which transmit from animals to humans and cause severe respiratory diseases in afflicted individuals (Fehr et al., 2017).

In 2002 in Guangdong province, China, the emergence of SARS began and subsequently, it was globally spread, causing 8096 cases and 774 deaths (De Wit et al., 2016). It seems that natural reservoirs for SARS-CoV are Chinese horseshoe bats (Li et al., 2005). Currently, no approved vaccines or specific antivirals are offered to cure SARS, and in the course of time the SARS pandemic in 2002 and 2003 was finished due to patient isolation and travel restrictions (Hoffmann et al., 2020).

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https://doi.org/10.1016/j.meegid.2020.104669
Received 5 October 2020; Received in revised form 9 November 2020; Accepted 4 December 2020
Available online 7 December 2020

Then a new infectious respiratory disease started from Wuhan, Hubei province, China in December 2019 (Wang et al., 2020), which seemed to be related to Huanan seafood market and as a result, human-to-human transmission occurred (Chan et al., 2020). The related respiratory disease that is termed coronavirus disease 19 (COVID-19), spread within China very fast and the virus was named SARS-coronavirus 2 (SARS-CoV-2) due to its close relation to SARS-CoV. By the time of writing this paper, the SARS-CoV-2 produced a severe lung disease in afflicted patients in China and 24 other countries due to international travels (Matsuyama et al., 2010).

Prostate cancer (PCa) is a heterogeneous disease and can cause lesions that might remain localized for long periods. However, sometimes aggressive forms of prostate cancer occur that have the potential to metastasize into bones and lymph nodes. Being the second most diagnosed worldwide cancer among men (mainly >65 years), makes PCa a public health concern in developed countries (Mottet et al., 2018).

The transmembrane protease serine 2:vets erythroblastosis virus E26 oncogene homolog (TMPRSS2:ERG) gene fusion has been assessed as a specific biomarker for PCa since 2005 (Park et al., 2014). TMPRSS2 is located at 21q22.2 that is detected to be expressed in both malignant and normal prostatic epitheliums. Furthermore, ERG is a member of the *E*-twenty-six (ETS) family, which are known to be the main regulators of differentiation, apoptosis, embryonic development, cell proliferation and inflammation (García-Perdomo et al., 2018). Both SARS-CoV and MERS-CoV are able to enter into the cells through endocytosis and are activated after entrance by using the cathepsin in endosomes (Maekawa et al., 2014), moreover, it is documented that expression of TMPRSS2 increases the replication and consequently the formation of these viruses in vitro and in vivo (Leyten et al., 2014). Also, it has been shown that TMPRSS2 might be the vital protease for new SARS-CoV-2 replication and many researches propose that this molecule can be a promising candidate for controlling the new virus (García-Perdomo et al., 2018).

SARS-CoV-2 spread also depends on TMPRSS2 activity (Iwata-Yoshikawa et al., 2019). Also, TMPRSS2-ERG is recognized as an important factor in fusion-positive PCa and this fusion protein causes changes in gene expression level. Therefore, this review article aims to gather the important facts in order to address the possibility of the relation of prostate cancer to the increased pathogenicity of SARS-CoV2.

2. Prostate cancer

Prostate cancer is the most frequently diagnosed male cancer and is the second cause of cancer deaths in North America (Jemal et al., 2004). Androgen receptor (AR) starts a cascade of transcriptional programs which in normal and malignant prostate tissue have a critical role in growth and survival. In order to cure the locally advanced, relapsed, or metastatic prostate cancer, the treatment regimens are based on inhibiting AR activity and function in patients. Although this method seemed to be effective at first, it could not completely cure the cancer and, further, a resistant form of prostate cancer to hormonal manipulations appears. There is increasing evidence that suggests AR through aberrant mechanisms can retain its activity and many of the AR target genes that are increasingly expressed for maintenance of prostate cancer development are still expressed (Dehm and Tindall, 2006). Consequently, failure to treat the prostate cancer results in metastasizing into the bones and lymph nodes in advanced cancers. Therefore, the treatment is composed of antagonizing the AR stimulus in order to stop feeding the tumor via chemical or surgical hormone ablation therapy (Galbraith and Duchesne, 1997).

In some cases, antiandrogen therapy results in the development of AR-independent cancer. It is observed that some AR-regulated genes such as PSA (prostate-specific antigen), that had decreased due to hormone ablation therapy, increase again in AR-independent tumors (Akakura et al., 1993) and accessory pathways such as TKR (tyrosine kinase receptors) are activated as an alternative to the androgen signal (Yeh et al., 1999).

The normal prostate is composed of three different regions. The cells of these zones vary considerably in their tendency to contributing to prostate cancer. For instance, 20% of prostate adenocarcinomas are related to transition zone that comprises 5%–10% of glandular tissue. The central zone cells rarely contribute to prostate cancer (1–5%) and involves about 25% of glandular tissue. Finally, the peripheral zone that is responsible for about 70% of cancers composes the majority of prostate tissue (70%) (Dehm and Tindall, 2006).

Cancer cells are largely dependent on androgens for development and survival, regardless of the origin of the neoplasm. Therefore, if operation is not remedial, castration and/or using AR antagonists are the backbones of systemic therapy. Primarily, androgen ablation causes noticeable AR inhibition and concomitant tumor regression, due to decrease in the expression of target genes such as PSA (Feldman and Feldman, 2001). By the way, the majority of prostate cancers revert to a resistant form that is unaffected by these hormonal manipulations, and further treatment is inevitably needed (Grossmann et al., 2001). The disease at this stage is denoted as androgen depletion-independent (ADI), androgen-independent, or androgen-refractory (Roy-Burman et al., 2005). Although ADI prostate cancer is resistant to additional efforts for blocking androgen action, the AR still remains a critical issue for the growth and development of most of these tumors and the majority of ADI prostate cancers has high levels of AR expression and also, further expression of PSA (Litvinov et al., 2003).

Research findings propose that ADI prostate cancer cells continue to proliferate and survive through aberrant mechanisms of AR activation, and therefore the AR signaling axis continues to be a critical target for therapy (Dehm and Tindall, 2006).

3. Androgens and androgen receptors

Androgens are a group of molecules that apply their functions through AR. Leydig cells in the testes are responsible for testosterone production which is the most abundant (90%) androgen in the blood circulation. Androgens produced by the adrenal cortex, such as dehydroepiandrosterone (DHEA) and androstenedione (4-dione), make up the remaining 10%. Both DHEA and 4-dione are converted to testosterone in peripheral tissues (Labrie et al., 2001). The AR is a 110 kDa phosphoprotein and member of the nuclear receptor transcription factor superfamily and are essential for normal development and function of prostate. Also this molecule shares a communal modular structure with other nuclear receptors, containing an N-terminal transactivation domain, a central DNA binding domain, and a C-terminal ligand binding/transactivation domain (Heinlein and Chang, 2004).

Activation of AR consequently renders, to the testicular synthesis of testosterone, its transport to target tissues, and the conversion by 5α-reductase type I and II to the more active metabolite 5-dihydrotestosterone (DHT) (Navarro et al., 2002). DHT is a more effective AR ligand than testosterone since it dissociates more gradually from the AR and produces a receptor conformation more resilient to degradation (Heinlein and Chang, 2004). In detail, by binding to AR, testosterone and DHT exert their biological effects via AR transcriptional activity. The AR activity is modulated by the interaction with coregulators and also, phosphorylation of AR and its coregulators (Buchanan et al., 2001; Heinlein and Chang, 2002). After attaching to androgen, a modification in the conformation and composition of AR happens, which leads to AR nuclear translocation. In the nucleus, the AR binds androgen response elements (AREs) as a dimer in the promoter and enhancer regions of various target genes (Heinlein and Chang, 2004) (Fig. 1).

Some of the coactivators are also vital for transcriptional activation of other steroid hormone receptors, such as the p160 family (SRC-1, GRIP1/ TIF2, RAC3/ pCIP/ ACTR/ AIB1/ TRAM1), P/CAF, CBP, and p300 (Grossmann et al., 2001). These coactivators possess intrinsic histone acetyltransferase (HAT) activity, which can be directed toward histone as well as other proteins (Roth et al., 2001). In addition to coactivators with HAT activity, the AR has been shown to specifically

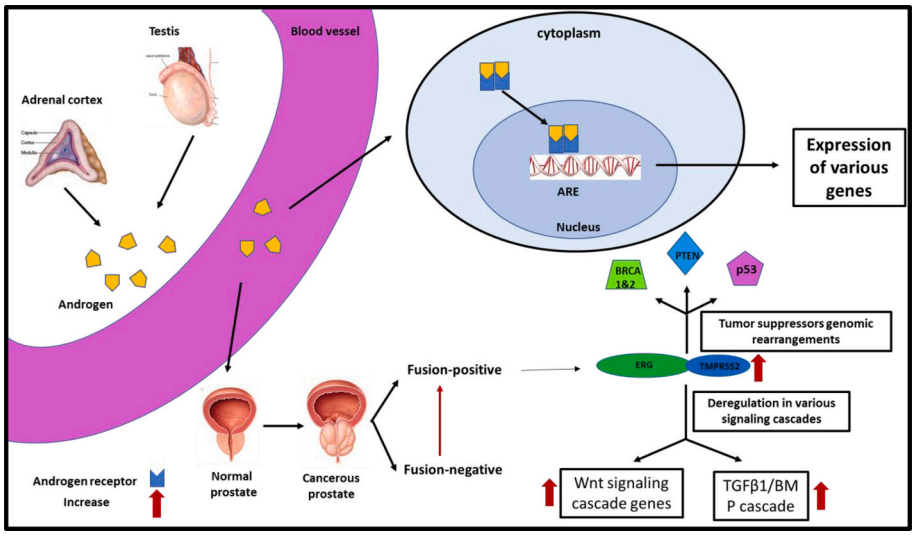

Fig. 1. The functional pathway of androgens and its receptor.

recruit the AR-associated (ARA) coactivators ARA70, ARA55, and ARA54 (Grossmann et al., 2001). The AR-induced assembly of these multi-protein complexes results in a finely regulated level of target gene transcription (Dehm and Tindall, 2006).

Studies indicate that by any method for treatment of prostate cancer (such as treatment with LHRH agonists and surgical castration) the serum levels of testosterone decrease about 90–95% while the intra-prostatic DHT levels decline by roughly 50% (Denis and Griffiths, 2000). Though this decrease is able to bring about the death of more than 70% of normal prostate secretory epithelial cells, the surviving prostate cancer cells would be exposed to a relative abundance of DHT. In contrast, GnRH agonist treatment has been described to cause reduction in intraprostatic DHT, about 90% (Forti et al., 1989). Combined treatment of castration and flutamide has been found to reduce prostate DHT levels to approximately 20% of pretreatment levels (Hida et al., 2008).

3.1. TMPRSS2 and androgens

Recognition of the TMPRSS2 gene that is a transmembrane serine protease was the result of using a subtractive hybridization method (Paoloni-Giacobino et al., 1997). TMPRSS2 is a type II transmembrane protein that has an extracellular COOH terminus containing the protease domain and an intracellular NH2 terminus (Lin et al., 1999). TMPRSS2 protein is vastly expressed in prostate secretory epithelium and in prostate cancer and the protein expression is also dependent on an androgen signal. The protease domain is released via an autocatalytic cleavage mechanism. Studies demonstrate that the highest expression of TMPRSS2 is at the apical side of prostate and prostate cancer secretory epithelia and within the lumen of the glands. Also, it was detected in colon cancer and pancreas samples. Collectively, data reveal that TMPRSS2 is a secreted protease that is highly expressed in prostate and prostate cancer, making it a possible target for diagnosis and therapy of cancer (Afar et al., 2001).

The usual molecular sign of prostate cancer is TMPRSS2-ERG gene fusions. Although remarkable advances have been made in unraveling various facets of TMPRSS2-ERG-positive prostate cancer, many unanswered questions still remain to be answered and further studies in order to elucidate the detailed function of TMPRSS2-ERG target genes and proteins in response to numerous stimuli in TMPRSS2- ERG fusion-positive prostate cancer cells are needed (Farooqi et al., 2014) (Fig. 1).

3.2. TMPRSS2-ERG fusion in normal and cancerous prostate cells

Studies have shown that the TMPRSS2-ERG fusion seems to be detectable in both late stage and benign hyperplasia as well as in the normal margin of prostate tumors (Lee and Swanton, 2012; Marusyk et al., 2012; Brabletz, 2012). Furthermore, detection of TMPRSS2-ERG fusion transcript was reported in 73% and 43% of primary prostate tumor samples and samples collected from non-malignant tissues, respectively (Clark et al., 2007).Incidentally, in normal and malignant prostate cells, the level of this fusion protein is different and even the level of TMPRSS2-ERG fusion transcript varies in different established prostate cancer cell lines (human prostate cancer VCaP and LNCaP cells are TMPRSS2-ERG positive and negative, respectively). Also, methylation of TMPRSS2-ERG fusion gene is a determinative factor in regulating the expression level of this molecule. For instance, fusion negative tumors are severely methylated in comparison to fusion positive ones (Börno et al., 2012).

3.3. Signal transduction cascades in fusion-positive prostate cancer

Various signal transduction cascades were deregulated in fusion-positive prostate cancer patients. Development of PCa would be facilitated through a sequence of explicit genetic alterations that might be summarized as early clonal expansion, genomic instability, inactivation of tumor suppressor (TS) genes, oncogenes overexpression, and distraction of the spatial-temporal function of signaling cascades (Fodde et al., 2001). As previously mentioned, the gene fusion in chromosome 21 that happens between the TMPRSS2 and ERG genes, results in the prostate cancers being divided into “fusion-positive” and “fusion-negative” (Clark and Cooper, 2009). This causes the expression of ERG transcription factor (TF) to be regulated via TMPRSS2 (an androgen responsive element) promoter. Therefore, TMPRSS2-ERG fusion protein might attach to ERG gene promoter and cause the overexpression of wild-type ERG. However, this process is also regulated by polycomb proteins that can control the hypermethylation of ERG promoters. The data cause ERG gene to appear as a hotspot of DNA methylation, especially in prostate cancer cells (Schwartzman et al., 2011).

To illustrate the exact function of TMPRSS2-ERG fusion protein several studies have been carried out. It was reported that in VCaP cells, targeted inhibition of TMPRSS2-ERG transcript is the reason of the remarkable decrease of ERG, while the result of constant transfection of TMPRSS2-ERG in the TMPRSS2-ERG deficient PC3 cells, was detected as an increase in ERG transcript. These data offer obvious evidence of ERG overexpression in fusion positive prostate cancer cells (Mani et al., 2011).

Furthermore, direct evidences that support the idea of regulation of AR by ERG protein exist. In ERG-negative and normal ERG expressing

prostate cancer cells, the signaling pathway that is activated ERG does not impose repressive effect on the expression of AR (Hoogland et al., 2012). But another study showed that in prostate cancer VCaP cells, ERG can suppress AR expression level by binding to AR (Yu et al., 2010). In addition, TMPRSS2-ERG fusion recruits in normal and also tumor cells after androgen treatment (Bastus et al., 2010). In a research, by culturing xenografts of male nude mice in vivo via serial transplantation the correlation between TMPRSS2-ERG fusion and androgen was investigated and overexpression of TMPRSS2-ERG was detected in all androgen-dependent xenografts. More importantly, they observed that although AR-negative tumors have the gene encoding for TMPRSS2-ERG fusion protein, this fusion gene has no expression (Hermans et al., 2006). Moreover, genes related to WNT and TGFB1/BMP (transforming growth factor beta 1/bone morphogenetic protein) transduction cascades are detected to be overexpressed in prostate tumors (Brase et al., 2011). Furthermore, in the process of genomic rearrangements during development of prostate cancer tumors, some tumor suppressor genes including BRCA1 (breast cancer 1, early onset) and BRCA2, p53, PTEN (phosphatase and tensin homolog) are activated (Mao et al., 2011). The next section gives a more detailed discussion of this subject (Fig. 1).

3.4. Overexpressed genes in fusion-positive prostate cancer cells

In comparison to TMPRSS2-ERG fusion-negative prostate cancer cells, some proliferation-related genes were observed with an increase in expression level in fusion-positive ones. Furthermore, although some treatments such as anti-androgen therapies and chemical castration are able to somehow reduce the expression level of some of these genes, these treatments seem to be inadequate (Lehmusvaara et al., 2012).

Research to better understand the biology of prostate cancer has elucidated that ERG up-regulation is zone-dependent and has been shown to be overexpressed in the glands of the peripheral zone rather than the transitional zone (Shaikhibrahim et al., 2012). Furthermore, analysis of the expression level of deregulated genes specified that the expression level of these genes in fusion-negative prostate tumor cells is more comparable to normal controls. At the same time, the expression level of gene expression in fusion-positive prostate tumors displayed a different and dissimilar pattern that correlated with the occurrence of fusion transcripts in prostate cancer. For example, ERG expression pattern was related to expression level of MMP9 (Metalloproteinase 9) and Plexin A2 that are engaged in the migratory potential and invasive capacity of cancerous cells (Tian et al., 2014), for more details, Table 1 summarizes the difference in expression level of genes in normal, fusion positive and fusion negative cells. The results in Table 1 elucidates how TMPRSS2-ERG encoded fusion proteins are able to impair checkpoints of the cell cycle and promote proliferation.

3.5. miRNA mediated cascade for regulating the AR

Previously, it was shown that overexpression of AR might cause antiandrogen resistance by amplifying signal output and changing the common response to antagonists (Chen et al., 2004). However, it is also imperative to mention that the loss of AR regulating miRNA signatures is a central aspect that underlies AR overexpression. For instance, it has been reported that androgen-induced AR binds to the miR-21 promoter, suggesting direct regulation transcription process and considerable prostate carcinogenesis. Nevertheless, miR-21 inhibition resulted in uncontrolled cellular proliferation decrease (Ribas et al., 2009). Also, a study has indicated that various miRNAs act as tumor suppressors and transiently transfecting cells with miR-331-3p reduced phosphorylated v-akt murine thymoma viral oncogene homolog 1 (AKT1) content (Epis et al., 2009).

Additionally, another important receptor, the ERBB2 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog) is dysregulated in prostate cancer. It was reported that overexpression of ERBB2 activated AR pathway in an

Table 1
The difference in expression pattern of genes in normal, fusion positive and fusion negative cells.

Gene name	Function	Relation to TMPRSS2-ERG gene fusion	Ref.
PRDX3 and 4	Upregulates in prostate cancer tissue	Influences on the prostate tumor's growth/negatively correlated with the level of the TMPRSS2-ERG gene fusion	(Li et al., 2012)
PARP1 and DNA-PKcs	Overexpressing ERG in normal prostate cell line with low endogenous ERG (RWPE)	ERG-overexpression	(Li et al., 2003)
ETS	Upregulates in primary prostate epithelial cells	Induce DNA double strand breaks in terms of γ-H2AX foci	(Li et al., 2003)
VDR	Prostate tumors with high levels of VDR	Twice as likely to be TMPRSS2-ERG fusion-positive	(Gu et al., 2005)
IL1R2, SPINT1, ZEB1 and 2	AR treated-immortalized primary prostate epithelial (EP) cells	TMPRSS2-ERG bound promoters of gene	(Ordovás et al., 2013)
PSMA	Upregulated in the adenocarcinoma of prostate cancer	TMPRSS2-ERG positive cells have a different gene network as treatment of VCaP cells with androgen analog resulted in the suppression of PSMA	(Haga et al., 2008)
WNT-associated pathway genes	ERG overexpression and nuclear translocation activate Wnt signaling	Via strongly histone deacetylase 1 (HDAC1)-positiveness and Suppression of tumor necrosis factors and cell death pathways	(Menachery et al., 2019; Simmons et al., 2005)
CRISP3	CRISP3 gene expression was associated with the ERG condition	TMPRSS2-ERG fusion-positive prostate tumors as compared to normal tissue	(Gierer et al., 2013)
PIM1	A serine/threonine kinase which is frequently upregulated in prostate cancer	TMPRSS2-ERG directly attach to the PIM1 promoter and results in overexpression of PIM1 upregulates modified cyclin B1 levels	(Zhou et al., 2015)
CACNA1D	An ERG target gene	Upregulated in TMPRSS2-ERG positive prostate cancer cells	(Gu et al., 2005)
OPN	An extracellular matrix glycophosphoprotein involved in the metastasis	ERG stimulates OPN expression by targeting ETS binding sites in the OPN promoter	(Kim et al., 2006)
TLR4	Cellular receptor	Induced by TMPRSS2-ERG encoded fusion products	(Kawase et al., 2012)
ILK	In BPH-1 and RWPE-1-fERG cells	ERG level was found to be associated with the overexpression ILK and its downstream effector of LEF1.	(Liu et al., 2006)
c-myc	A family member of regulator and proto-oncogenes that code for transcription factors	In TMPRSS2-ERG fusion-positive prostate cancer cells	(Gao et al., 2013)
TDRD1	In ERG overexpressing prostate cancer cells	ERG enhances the expression of this gene by controlling the methylation status of the promoter region	(Goren et al., 2020)
CXCR4	In prostate cancer cells	IKK and AKT kinases were noted to phosphorylate ERG at Serine 81 and 215, phosphorylated ERG regulated expression of CXCR4	(Khomich et al., 2018)

PRDX (Peroxiredoxins); PARP1 (poly ADP-ribose polymerase 1); DNA-PKcs (protein kinase, DNA-activated, catalytic polypeptide); ETS (E-twenty-six); VDR (vitamin D (1,25-dihydroxyvitamin D3) receptors); IL1R2 (Interleukin 1 receptor, type II); SPINT1 (serine peptidase inhibitor, Kunitz type 1); ZEB (zinc finger E-box binding homeobox); PSMA (Prostate-specific membrane antigen); WNT (wingless type MMTV); CRISP3 (cysteine-rich secretory protein 3); PIM1 (pim-1 oncogene); CACNA1D (calcium channel, voltage-dependent, L type, α-1D subunit); OPN (Osteopontin); TLR4 (Toll-like receptor 4); ILK (integrin-linked kinase); LEF1 (lymphoid enhancer-binding factor 1); TDRD1 (Tudor domain-containing protein 1); IKK (I kappa B); CXCR4 (chemokine (C-X-C motif) receptor 4).

androgen-deficient environment in cancer cells (Berger et al., 2006). Another research group has indicated that ERBB2/ERBB3 can maintain AR protein levels and ERBB2/ERBB3 were found to be attached to the promoter/enhancer of androgen-regulated genes in hormone-refractory prostate cancer. ERBB2 and ERBB3 considerably increase the androgen-dependent AR transactivation of reporter genes in prostate cancer cells (Gregory et al., 2005). Therefore, using miR-331-3p that can repress ERBB2 expression by targeting the U-rich element located in the ERBB2 3′- UTR (untranslated region), the expression of ERBB2 was suppressed. Further studies demonstrated that in TMPRSS2-ERG positive prostate cancer cells this miRNA mediated regulation is lost and results in the AR and ERBB2 expression which cooperatively prompt the expression of cancer promoting genes (Epis et al., 2011).

It was observed that ERG can control the migratory potential of prostate cancer cells through binding to the promoter region of CXCR4 and ADAMTS1 (ADAM metallopeptidase with a thrombospondin type 1 motif, 1) genes (Carver et al., 2009). By the way, it is reported that CXCR4 expression can be suppressed by miR-139. Therefore, dysregulation of miR-139 negative control in cancer cells (that is proved to happen gastric cancer cells by interaction of ERBB2 with CD44) might result in increased risk of cancer (Bao et al., 2011).

Another microRNA that deals with AR is miR-23a27a24-2 cluster, whose maturation from pri-miR-23a27a24-2 to mature pre-miR-23a27a24-2 is controlled partially by association of AR to its promoter that leads to starting temporary transcription via enhanced androgen-induced processing. Particularly, miR-27a negatively regulates AR by controlling prohibitin (a corepressor) and due to its ability is perceived as a promising candidate for treatment of PCa (Fletcher et al., 2012).

Some other microRNAs that can downregulate the transcriptional activity of AR, are miR-488 and miR-let-7c (Nadiminty et al., 2012). Also, three microRNAs named miR-130a, -203 and -205, cooperative in order to target the members of MAPK (mitogen activated kinase-like protein) and AR pathway of signaling (Boll et al., 2013). Furthermore, HNRNPK (heterogeneous nuclear ribonucleoprotein K) and VEGF-A are directly targeted by miR-205 and miR-29b, respectively (Szczyrba et al., 2012). These genes are able to cooperatively inhibit translation of AR (Mukhopadhyay et al., 2009). Similarly, CD44 and AKT2 are direct targets of miR-708 (Saini et al., 2012).

Finally, some reports have proved that different miRNA subsets modulate PTEN, that results in retaining AKT cancer promoting ability. PTEN that is negatively regulated by miR-153 and miR-21 (Wu et al., 2013) in prostate cancer, is observed to be the target of other miRNAs in other cancers such as: miR-21, miR-221 and miR-222 in gastric cancer (Zhang et al., 2012); miR-93 in ovarian cancer (Fu et al., 2012); miR-519d in liver cancer (Fornari et al., 2012).

There are other miRNAs that can regulate the transcriptional activity of AR and its target genes such as miR-29a and miR-1256 that in their demethylated status target TRIM68 (tripartite motif containing 68). Then, TRIM68 interacts with AR and enhances transcriptional activity of the AR target genes (Li et al., 2012).

4. SARS-CoV2 entrance mechanism

The entrance of coronaviruses is facilitated by spike (S) protein. This protein is composed of two parts, S1 and S2. The S protein is cleaved at the S1/S2 and the S2' sites and the result of priming the S protein is S1 and S2. S1 part is responsible for binding the virus to the host cell surface and S2 allows fusion of viral and cellular membranes (Hoffmann et al., 2020) (Fig. 2). The entry receptor of host cells which is related to this process is angiotensin-converting enzyme 2 (ACE2) in SARS which uses the cellular enzyme TMPRSS2 (a serine protease) for S protein priming (Matsuyama et al., 2010; Li et al., 2003).

SARS-CoV infects primarily macrophages and pneumocytes in the lung. However, ACE2 expression is not limited to the lung, and extrapulmonary spread of SARS-CoV in ACE2+ tissues, was observed (Gu et al., 2005). As the SARS-S and SARS-2-S share 76% amino acid identity in their sequences, it seems that SARS-2-S might use the same entrance mechanism (ACE2 and TMPRSS2) for entry to the host cells (Hoffmann et al., 2020).

It seems that SARSCoV-2 in comparison to SARS-CoV, is more transmissible, and this might be related to the higher efficiency of SARSCoV-2 in cellular attachment that renders robust infection of ACE2+ cells in the upper respiratory tract (Ordovás et al., 2013). By the way, it is important to consider that SARS-s has the ability to down-regulate ACE2 expression that in normal condition protects lung from injury. This regulation might have promoting effects in the disease progression. If SARS-CoV-2 is able to undergo this regulatory pattern, it would be the other reason for its greater pathogenicity (Haga et al., 2008).

4.1. S protein priming details

Coronavirus S proteins priming that is organized by host cell proteases is critical for entry of viral particles into the host cells. The proteases cleave S protein into S1 and S2 parts via several arginine residues (multibasic) which are characteristic of cleavage sites at S1/S2 and S2' priming positions of SARS-2-S that confer high cleavability potential to the sites (Fig-2). Owing to this efficient cleavability, SARS-2-S is efficiently cleaved, and cleaved S proteins incorporates into VSV particles. It seems important to mention that this effective multibasic cleavage site does not exist in RaTG13 coronavirus (most closely related to SARS-CoV-2) and might be a critical advantage for SARS-S2 pathogenicity due to

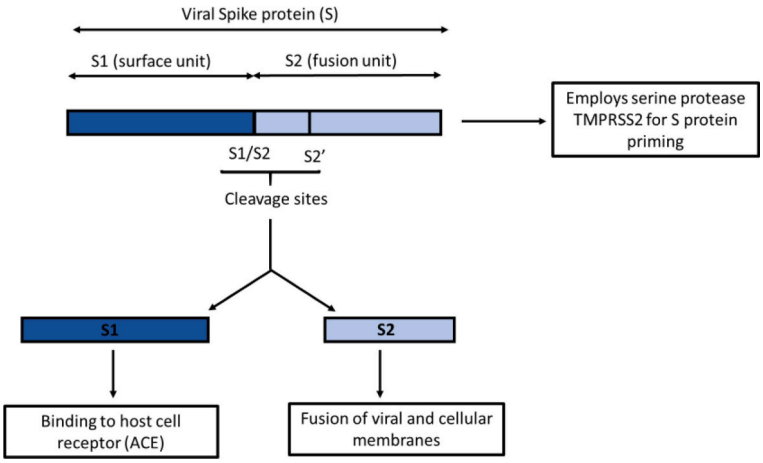

Fig. 2. The S protein of coronaviruses entrance to target cells.

effective entrance to the host cells (Menachery et al., 2019).

In TMPRSS2- cells SARS-CoV can use CatB/L enzyme which is an endosomal protease for S protein priming (Simmons et al., 2005). But it is important to consider that S protein priming by TMPRSS2 and not CatB/L is crucial for viral entrance to target cells and is also spread in the infected host cells (Iwata-Yoshikawa et al., 2019).

Studies indicate that SARS-CoV-2 is dependent on TMPRSS2 activity for entrance and subsequent infection of the host cells. Altogether, it seems that TMPRSS2 is a host cell factor that is important for the spread of some clinically related viruses such as coronaviruses and influenza A viruses (Matsuyama et al., 2010; Gierer et al., 2013; Zhou et al., 2015). However, TMPRSS2 seems to be a dispensable factor for development and homeostasis in host cell (Kim et al., 2006). Therefore, this criterion makes it an attractive drug target candidate. In this regard, camostat mesylate is a serine protease inhibitor that can block TMPRSS2 activity and has been approved in Japan for an unrelated indication previously (Zhou et al., 2015; Kawase et al., 2012). Moreover, convalescent SARS patients exhibit a neutralizing antibody response that can be detected even 24 months after infection and that is largely directed against the S protein (Liu et al., 2006).

5. The possible relation of prostate cancer to respiratory viral infections such as covid-19 pathogenesis

It is known that TMPRSS2-ERG gene fusion has been assessed as a specific biomarker for PCa (Park et al., 2014). Also, it was determined that both SARS-CoV and MERS-CoV, are able to enter into the cells by the help of TMPRSS2-ERG gene and furthermore, it is documented that expression of TMPRSS2 increases the replication and consequently formation of these viruses in vitro and in vivo (Leyten et al., 2014; Gao et al., 2013). Additionally, it has been shown that TMPRSS2 might be the vital protease for new SARS-CoV-2 replication and a great deal of research propose that this molecule can be a promising candidate for controlling the new virus (García-Perdomo et al., 2018). As the SARS-S and SARS-2-S share 76% amino acid identity in their sequences, it seems that SARS-2-S might use the same entrance mechanism (ACE2 and TMPRSS2) for entry to the host cells (Hoffmann et al., 2020).

The high expression rate of TMPRSS2-ERG in different tissue parts and cells of normal and cancerous prostate such as apical side, secretory epithelia and within the lumen of the glands make this molecule a promising target for cancer therapy and diagnosis (Afar et al., 2001). Therefore, understanding the activation and repressing effect of this molecule on other target genes and proteins in response to several stimuli might be sequentially gathered and re-interpreted (Farooqi et al., 2014).

A lot of hard work is being directed toward the identification of molecules that can be helpful in the management of COVID-19. As previously mentioned, TMPRSS2-ERG fusion molecule would increase in both fusion-positive and negative types of prostate cancers (Lee and Swanton, 2012; Marusyk et al., 2012; Brabletz, 2012) and this change seems to make these patients better candidates for SARS-CoV-2 disease. Furthermore, elevation in infected males with androgen related baldness to SARS-CoV-2 disease (Goren et al., 2020) might certify the possible role of this molecule in facilitating the SARS-CoV-2 infections development in these patients. Additionally, researches show that genes' expression during prostate cancer are affected by TMPRSS2-ERG fusion protein, and might have some relation to viral respiratory infections. As an illustration, peroxiredoxins such as PRDX3 and 4 are a ubiquitous family of antioxidant enzymes that can regulate cytokine-induced peroxide levels and thus interfere in signal transduction. In infected cells with respiratory viruses, redox homeostasis show changes which are linked to inflammation and subsequent tissue damage. The virus can induce the production of ROS (reactive oxygen species) which disturb the host balance of redox. These imbalances are central triggers of inflammation in various ways, for instance, by induction of ROS-generating enzymes and disturbance of antioxidant defense. Nevertheless, our knowledge about the systematic mechanism of virus-associated oxidative stress and the following consequences for cells, tissue, and the organism is not enough. Many conflicting data on the antioxidant defense status and role of ROS in viral propagation exist and need to be resolved based on in vitro as well as clinical studies (Khomich et al., 2018).

ADP-ribosylation that is a post-translational modification, enables the host response to virus infection. Several viruses, as well as all members of the coronavirus family, encode a macrodomain to inverse ADP-ribosylation and fight this immune response. As such, viruses with mutations in the macrodomain are highly attenuated and cause minimal disease in vivo (Grunewald et al., 2019). Gharote et al. propose nicotinamide to be a potential PARP inhibitor and is helpful in prevention of cytokine storm in the lung parenchyma cells. Furthermore, they suggest that high doses of nicotinamide might moderate the outcome in COVID-19 (Gharote, 2020).

Furthermore, in primary prostate epithelial cells the upregulation ETS induce DNA double strand breaks that simplifies the ERG fusion potential. Then, the reverse process conducted by the usage of inhibition of PARP causes response to DNA damage in ETS-positive cancer cells (Brenner et al., 2011). As IL-1 is an inflammatory cytokine, that has a partial role in cytokine storm production during SARS-CoV-2 infection (Ye et al., 2020), increase in IL-1 receptors might help in development of infection. Assays revealed that TMPRSS2-ERG contain possible binding sites in promoters of IL1R2, SPINT1 and ZEB1 genes. TMPRSS2-ERG directly trans-activates ZEB1 while SPINT1 trans-activates and IL1R2 trans-represses trigger ZEB2 expression in a direct manner (Leshem et al., 2011).

Another study found that the expression of ACE2 is limited to population of epithelial cells and is repressed by ZEB1. Also, ZEB1 plays a role in promoting the transition of epithelial cells to mesenchymal ones (EMT). Remarkably, during the infection of lung cancer cells, SARS-CoV-2 metabolic and transcriptional changes consistent with EMT are induced, which results in upregulation of ZEB1, and downregulation of ACE2. These data suggest that a novel model of SARS-CoV-2 pathogenesis might possibly exist by which the cells that are infected by virus shift toward a progressive state of mesenchymal and lose *ACE2* expression, along with its acute respiratory distress syndrome-protective effect, in a ZEB1-dependent manner. It is also recommended that reduction of ZEB1 (as with bemcentinib), might offer a possible strategy to reverse this effect (Stewart et al., 2020).

Wnt/β-catenin signaling is an essential pathway in cell cycle control. Previously, dysregulation of this pathway during viral infection has been reported. More et al., examined the effect of modulating this signaling pathway during influenza virus infection. The in vitro experiments in mouse lung epithelial E10 cells showed that this pathway is activated by Wnt3a during influenza infection and results in virus mRNA and viral particle production increase (More et al., 2018).

Pim1 is an oncogenic serine/threonine kinase. TMPRSS2-ERG can directly attach to the PIM1 promoter. Cyclin B1 modification is the consequence of overexpression of PIM1 through TMPRSS2-ERG upregulation (Magistroni et al., 2011). During HCV infection, NS5A protein might interact with Pim1 which contributes to Pim1 protein stability. This NS5A produced protein stability may be associated with HCV pathogenesis considering the fact that the expression level of Pim1 protein increases in many cancers. It is presented that Pim kinase is specifically essential for early entrance step of the HCV life cycle. Thus, it is suggested that Pim kinase acts as both an HCV cell entry factor and also as a new anti-HCV therapeutic target (Park et al., 2015).

An in vitro approach showed infected PBECs (primary bronchial epithelial cells) from healthy participants with HRV-16 (human rhinovirus-16) in the absence or presence of a highly specific pharmacological inhibitor for Pim1 kinase. Previously, it was perceived that Pim1 kinase is highly expressed in the bronchial airway epithelium and therefore, pharmacological inhibition of Pim1 kinase increases the sensitivity of bronchial epithelial cells to cell death upon challenge with

cigarette smoke extract. This study showed that by inhibiting Pim1 kinase activity, the viral replication and even release of viral particles in cultured PBECs reduces by developing the induction of cell death during viral infection (De Vries et al., 2015). It was found that ERG expression level was associated with the overexpression of ILK and thus, its downstream effector such as LEF1. Therefore, targeted inhibition of ERG might result in downregulation of the ILK and LEF1 gene expressions (Becker-Santos et al., 2012).

CVB3 (coxsackievirus B3) virus is known to be the most common agent for myocarditis. A study, reported that in CVB3-infected patients, inhibition of ILK cells increased the viability of infected cells significantly, which caused delay in viral replication and release. Complementary experiments revealed that the observed protective effect of ILK inhibition is dependent on the associated downregulation of virus-induced Akt activation. This study may convey new insights in trying to characterize an innovative therapeutic target for treatment of enteroviral myocarditis (Esfandiarei et al., 2007) (Fig. 3).

6. Conclusion

In PCa, androgen signaling usually regulates the expression level of genes associated with cancer cell increase and survival. Although androgen deprivation therapy is an alternative for the patients, by the way, the tumors that relapse and undergo castration therapy generally act as resistant prostate cancer phenotype that correlates with terrible analysis and excessive metastatic potential. Furthermore, androgen signaling has been involved in cancerous prostate cellular invasion and metastasis. Additionally, the expression level of TMPRSS2 protein has been strongly correlated with prostate cancers development. Still, the actual TMPRSS2 substrates and TMPRSS2 primary proteolytic cascade remain to be understood, and the precise function of TMPRSS2 in cancers progression continues to be unclear. The association between TMPRSS2-ERG fusion gene and the prognosis of prostate cancers has been detected and it is proposed that TMPRSS2-ERG be used as the gold standard biomarker for diagnosis and stratification of PCa.

Functional interdependencies have been proposed among the molecular components in fusion-positive prostate cancers cells and their relation to pathogenesis of viral infections especially respiratory

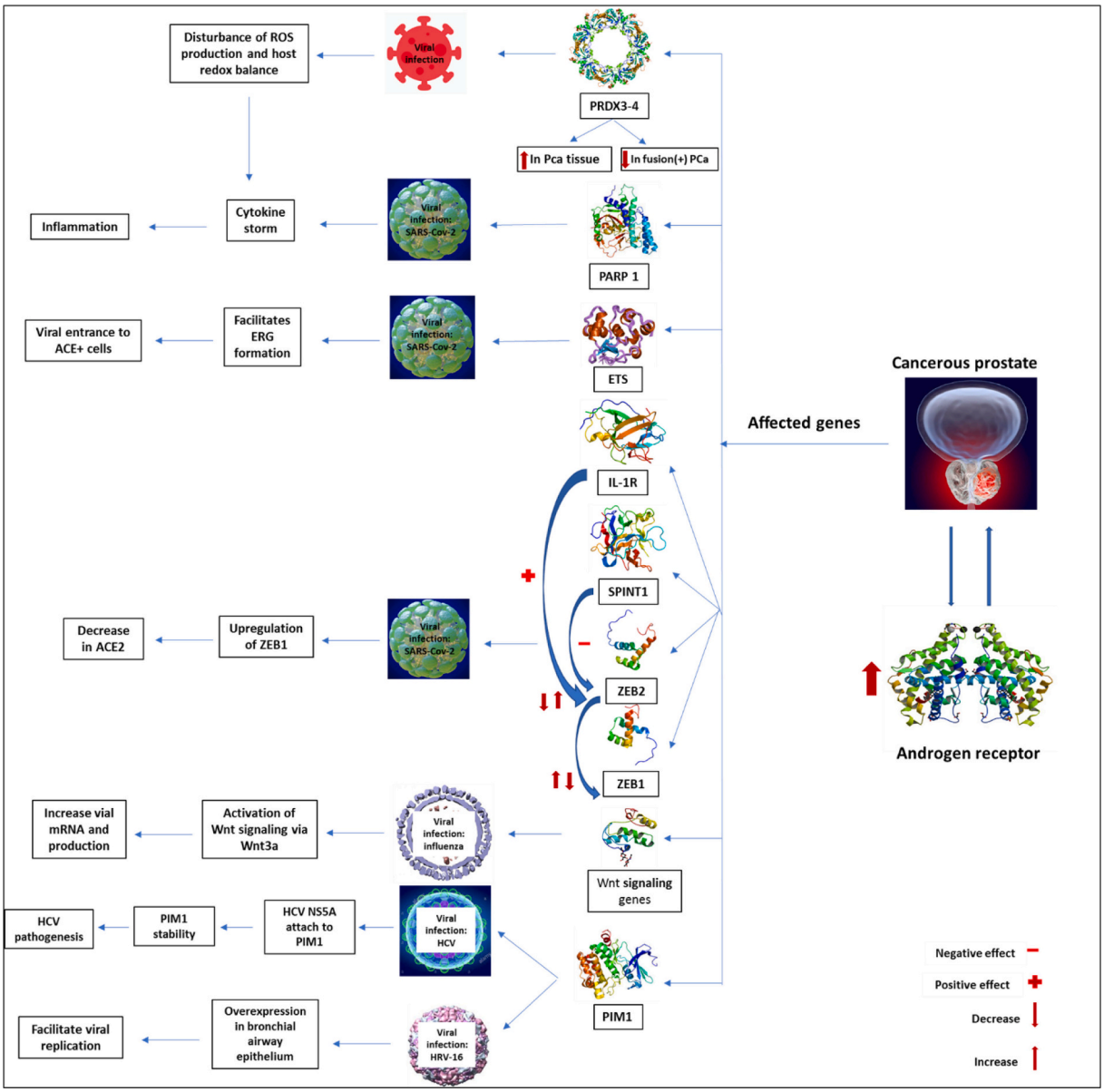

Fig. 3. The possible relation of prostate cancer to viral pathogenesis.

infections such as SARS-CoV-2. TMPRSS2 is critical for the development and homeostasis and consequently determines an attractive candidate drug target. The less investigated facet of dysregulated gene expression network during PCa needs extensive research to characterize the genomic and then proteomic content of fusion-positive prostate cancer cells. This review discusses the probable relation between fluctuated gene expression during PCa especially fusion positive and SARS-CoV-2 disease and pathogenesis.

Funding

This study was supported by Shiraz University of Medical Sciences (grant No. 22358-106-01-99). Funding sources had no influence over study design, data collection, analysis or interpretation or manuscript preparation and submission.

Authors' contributions

A. A. performed the majority of Collecting and writing of the data; A. A., S. J. and R. Y. performed the molecular investigations; A. A., S. J., R. Y. and J. R. designed and coordinated the research; A. A., S. J., R. Y. and J. R. and N. A. wrote the paper.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

Acknowledgements

The authors wish to thank Shiraz University of Medical Sciences for the support and funding preparation.

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