Genetic and molecular biology of bladder cancer among Iranian patients

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INTRODUCTION

Cancer is the third cause of deaths among Iranian population (Saadat et al., 2015). Almost 90,000 new cancer cases are diagnosed per year which is estimated to be doubled by the 2020 in this population. There is also different incidence of cancer in males and females in which more than 55% of patients were observed among Iranian males (Rafiemanesh et al., 2015). Bladder cancer (BC) is the 14th common cause of cancer-related deaths globally (Ferlay et al., 2015) and is the 6th most common malignancy among Iranians (Jafari-Koshki, Arsang-Jang, & Mahaki, 2017). BC is histologically categorized in three subtypes including transitional cell carcinoma (TCC), squamous cell carcinoma (SCC), and adenocarcinoma. Although TCC is the most common type of bladder cancer (90%) in developed countries, SCC is the most frequent type (75%) in developing countries (Pakzad et al., 2015). In Iran, bladder and papillary TCC include 43.89% and 49.86% of cases, respectively (Rafiemanesh, Lotfi, Bakhtazad, Ghoncheh, & Salehiniya, 2018). There is clear correlations between BC and several risk factors such as smoking, body mass index, chronic infections, and genetic factors (Afshari, Janbabaei, Bahrami, & Moosazadeh, 2017; Freedman, Silverman, Hollenbeck, Schatzkin, & Abnet, 2011; Jemal et al., 2011). Smoking, age, analgesic use, and hair dye were also the risk factors among Iranian cases (Ramezani,
Naderi, Almasi, & Sadeghi, 2016; Shakhssalim et al., 2010). The highest BC incidences are observed in developed and some African countries, whereas the Middle East and North Africa have the highest mortality rates (Chavan, Bray, Lortet-Tieulent, Goodman, & Jemal, 2014). BC is more common (about 4 times) among men compared with women that can be associated with higher smoking behaviors among men (Murta-Nascimento et al., 2007). The mortality rate of BC is also higher among men compared with women (Ahmadi et al., 2012). Recent reports have shown that there is a rising trend of BC incidence among Iranian population in which the total ASIR increased from 10.47 to 18.2 per 100,000 in both genders (Rafieimanesh et al., 2018). The standardized incidence rate is reported between 26.9 and 5.3 per 100,000 among European males and females, respectively (Ferlay et al., 2013). Whereas the rates are 14.42 and 3.78 among Iranian men and women, respectively, which are lower than European countries (Rafieimanesh et al., 2018). There is also a geographical variation in BC incidence in Iran in which the Yazd, Kurdistan, Gilan, and Fars provinces have the highest, whereas the Hormozgan, Hamedan, and Sistan-Baluchestan provinces had the lowest rates (Esmaeizadeh, Salahi-Moghaddam, & Khoshdel, 2015). About 20% of primary BC tumors have muscle bladder layer invasion and poor prognosis at the time of diagnosis. And there is a high ratio of tumor relapse after tumor resection (Goodison, Rosser, & Urquidi, 2013). Cystoscopy and urine cytology are the common diagnostic methods of BC (Goodison et al., 2013; Griffiths & Action on Bladder Cancer, 2013). However, small papillary tumors could be missed by standard white-light cystoscopy (WLC) which needs fluorescence and narrow-band imaging (NBI) cystoscopy (Cheung, Sahai, Billia, Dasgupta, & Khan, 2013). Therefore, regarding the different incidence ratios between different countries and areas, it is required to introduce population-based novel diagnostic and screening methods for the early detection of BC and high-risk cases. In present review we have summarized all of the reported genes among Iranian BC patients until now which were significantly associated with tumorigenesis (Table 1). Moreover, for the first time we categorized all of the reported genes based on their cell and molecular functions (Figure 1) to clarify the genetic and molecular biology of BC among Iranian population.

2 | APOPTOSIS AND CELL PROLIFERATION

Apoptosis is a programmed cell death involved in regulation of cell proliferation following DNA damage. Therefore, apoptosis aberration can be associated with tumor progression. Apoptosis is regulated by two protein families including BCL-2 and IAP. Survivin (BIRC5) (OMIM: 603352) belonged to the inhibitors of apoptosis (IAPs) family and is involved in regulation of apoptosis and cell proliferation (Ambrosini, Adida, & Altieri, 1997). Survivin is mainly expressed in tumor cells, with a rare expression in normal differentiated cells. It has been shown that the full-length survivin and survivin-2B isoforms were the highest and lowest expressed isoforms in bladder tissues. Moreover, the normal tissues had low levels of survivin and survivin-DE3 expressions. There was a significant association between the levels of survivin/survivin-DE3 expressions and tumor aggressiveness among a sample of Iranian BC patients (Atlasi, Mowla, & Ziaee, 2009). Another study has been reported that the recurrent bladder tumors had higher survivin and/or survivin-DE3 expression compared with primarily tumors among a subpopulation of Iranian patients (Mowla, Emadi Bayegi, Ziaee, & Nikpoor, 2005). The survivin and survivin-DE3 overexpressions resulted in declined 5 years survival rate among a sample of Iranian subjects. Moreover, the overexpression of survivin and survivin-DE3 was more frequent among high-grade and stage tumors. They also observed that the survivin-2B overexpression was correlated with decreased risk of mortality. Therefore, they introduced the survivin and survivin-DE3 isoforms as markers of aggressive and recurrence BC, whereas the surviving-2B isoform was protective (Nourae et al., 2009). P53 is a tumor suppressor involving in cell-cycle regulation and apoptosis (Esrig et al., 1994; Lane, 1992). It has been shown that there was significant difference in P53 (OMIM: 191170) expression between papillary urothelial neoplasms of low malignant potential (PUNLMP) and papillary low-grade TCC in which the P53 overexpression was more frequent among papillary low-grade TCC tumors (Kalantari & Ahmadnia, 2007). A mutational analysis of TP53 was performed among a group of Iranian BC patients which showed that a noticeable numbers of patients were carriers of deletion/duplication mutations. Majority of duplication and deletion changes were observed in exons 6 and 1 (Bazrafshani et al., 2016). Apoptosis is a critical cellular response toward genotoxic stress which sensitizes the tumors cells to chemotherapeutic drugs (Debatin, 2004). The BCL2 (OMIM: 151430) and BAX (OMIM: 600040) are anti- and proapoptotic regulators, respectively. It has been observed that the patients with shorter relapse-free time had high BCL2/BAX ratio expression in a sample of Iranian BC cases which introduced BCL2/BAX expression ratio as a significant prognostic marker of low-grade BC (Golestanl Eimani et al., 2014). Cyclooxygenases (COXs) are a family of myeloperoxidase catalyzing the prostaglandin synthesis from arachidonic acid (Chandrasekharan & Simmons, 2004). COX-2 (OMIM: 600262) is a critical factor during prostaglandins production and is involved in tumorigenesis through apoptosis inhibition, angiogenesis, and metastasis induction (Meric et al., 2006; Pruthi, Derksen, Gaston, & Wallen, 2004). COX-2 downregulates proapoptotic NO in tumor cells following the
**TABLE 1** All of the involved genes in bladder cancer susceptibility among Iranian patients

| Study (et al) | Year | Gene | Sample | Results |
|--------------|------|------|--------|---------|
| Atlasi       | 2009 | BIRC5| 30 Tumors, 28 Controls | Overexpression |
| Mowla        | 2005 | BIRC5| 17 Patients | Overexpression |
| Nourae        | 2009 | BIRC5| 30 Patients | Overexpression |
| Kalantari    | 2007 | P53  | 50 Patients, 10 Controls | Overexpression in papillary low-grade TCC |
| Bazrafshani  | 2016 | P53  | 60 Patients | Mutation |
| Golestani Eimani | 2014 | BCL2, BAX | 40 Patients | BCL2/BAX expression ratio as prognostic marker |
| Tabriz       | 2013 | COX2 | 92 Patients | Correlation with age, grade, and lymph node |
| Shakhsalim   | 2013 | mtDNA| 26 N/T, 504 Controls | Polymorphism was correlated with BC risk |
| Jashidian    | 2008 | NMP22| 76 Patients, 75 Controls | Higher urine levels |
| Safarinejad  | 2011 | MTHFR| 158 Patients, 316 Controls | Polymorphism was correlated with BC risk |
| Shafiei      | 2019 | DCLK1| 472 Patients | Overexpression |
| Shafaroudi   | 2008 | BMI1 | 40 Patients, 8 Controls | Overexpression |
| Amini        | 2014 | BMI, NANOG | 10 Patients | Overexpression |
| Atlasi       | 2007 | OCT4 | 32 Tumors, 22 Normal | Overexpression |
| Hatefi       | 2012 | OCT4 | 30 Patients | Correlation with grade and stage |
| Keymoosi     | 2014 | ALDH1A1, CD44 | 159 Patients | ALDH1A1 was correlated with grade, stage, and age |
| Nekooheesh   | 2018 | miR-10b, miR-34b, miR-103, miR-141 | 66 Patients, 53 Controls | miR-10b, miR-34b, and miR-103 overexpressions, miR-141 underexpression |
| Khosnevisan  | 2015 | miR-886-5p | 70 Patients | miR-886-5p overexpression in high-grade BC |
| Mahdavinezhad| 2015 | miR-200c, miR-30b, miR-141 | 35 N/T | Overexpression |
| Ghorbanmehr  | 2019 | miR-21-5p, miR-141-3p, miR-205-5p | 45 Patients, 22 Controls | miR-21-5p, miR-141-3p, and miR-205-5p urinary overexpressions |
| Mahdavinezhad| 2015 | miR-30b, miR-141, miR-200c | 35 N/T | Muscle-invasive BC had lower levels of expression |
| Ganji        | 2017 | miR-99a, miR-205 | 36 N/T | miR-99a and miR-205 underexpressions |
| Monfared     | 2013 | TGF-β, miR-21 | 30 N/T | TGF-β underexpression mainly in low-grade BC, miR-21 overexpression in high-grade BC |
| Ousati Ashtiani | 2017 | LINC00152, LINC01082 | 50 N/T | LINC00152 and LINC01082 underexpressions |
| Yazarlou     | 2018 | MALAT1, LINC00355, UCA1-203 | 59 Patients, 24 Controls | MALAT1, LINC00355, and UCA1-203 overexpressions in urinary exosomes |
| Bizhani      | 2018 | PIK3CA, AKT1, mTOR | 235 Patients, 254 Controls | Polymorphisms were correlated with BC risk |
| Ousati Ashtiani | 2018 | PIK3CA | 50 N/T | Mutation |
| Jalali Nadoushan | 2007 | HER-2/neu | 75 Patients | Overexpression in higher grade of TCC |
| Seyedabadi   | 2018 | CEP55, FOXM1, PLK1 | 36 Patients | CEP55, FOXM1, and PLK1 overexpressions |
| Ousati Ashtiani | 2017 | FGFR1, FGFR3 | 50 N/T | FGFR1 and FGFR3 overexpressions |
| Hashemi      | 2018 | SGSM3 | 143 Patients, 144 Controls | Polymorphisms were correlated with BC risk |

(Continues)
prostaglandin production (Cao & Prescott, 2002). It activates the PPAR through prostaglandin I2 (Breyer, Bagdassarian, Myers, & Breyer, 2001). The COX-2 inhibition results in impaired PPARδ activation which activates BAD proapoptotic factor (Liou, Ghelani, Yeh, & Wu, 2007). It has been shown that there were correlations among COX-2 expression, age, grade, and lymph node involvement among a subpopulation of Iranian BC patients. The high-grade tumors had higher levels of COX-2 expression compared with other grades (Tabriz, Olfati, Ahmadi, & Yusefnia, 2013). Mitochondria have a critical role in apoptosis regulation through modulation of Ca²⁺ signaling in which the mitochondrial Ca²⁺ accumulation leads to apoptosis. Mitochondrial DNA (mtDNA) contains several genes such as electron transport chain subunits, tRNAs, rRNAs, and a noncoding sequence (D-loop) (Suzuki et al., 2003). The D-loop regulates replication and transcription of mtDNA (Yu et al., 2007). Mitochondrial dysfunction is associated with various degenerative and metabolic disorders and cancer. The germ line and somatic mtDNA mutations are linked with mitochondrial disorders and cancer, respectively. Regarding the lack of protective histones and DNA repair processes, mtDNA is more prone for the mutation accumulation compared with nuclear DNA. Mutational analysis of D-Loop sequences was performed among a subpopulation of Iranian BC patients compared with their corresponding normal margins. It has been shown that there was a significant correlation between D-loop C16069T polymorphism and BC (Shakhssalim et al., 2013).

Sustained proliferation is one of the hallmarks of cancer that can be observed by deregulation of cell growth and DNA replication. A normal DNA replication is required to maintain the genomic stability. Nuclear matrix proteins (NMPs) are nucleus structural proteins involved in DNA replication and gene expression (Pardoll, Vogelstein, & Coffey, 1980). It has been observed that the BC patients had higher levels of urine NMP22 compared with controls. Moreover, there were significant correlations between the urine levels of NMP22 and stage and grade. Therefore, they introduced urine NMP22 as a noninvasive and sensitive diagnostic method for BC among a subpopulation of Iranian cases (Jamshidian, Kor, & Djalali, 2008). Smoking is one of the main risk factors of BC. Reactive free radicals are the most important smoking-related carcinogens. Therefore, it is important for the smokers to have high intakes of antioxidants such as folate and B vitamins (B12, B6, and B2). MTHFR (OMIM: 607093) is involved in folate and vitamin B12 metabolisms and methionine production. Folate is a critical coenzyme during DNA synthesis and repair. It has been observed that there was an association between 1298AC and 1298CC genotypes of MTHFR and increased risk of BC among a subpopulation of Iranian patients. The 1298AA genotype significantly reduced BC risk. Moreover, the 677CT and 677CC genotypes were correlated with tumor aggressiveness. They observed that the 677CT-1298AC and 677CC-1298CC carriers had the highest BC susceptibility in this population (Safarinejad, Shafiei, & Safarinejad, 2011a).
SELF-RENEWAL

Cancer stem cells (CSCs) are a subpopulation of tumor cells with self-renewal and drug resistance characteristics which are associated with tumor progression and metastasis (Moghbeli, Moghbeli, Forghanifard, & Abbaszadegan, 2014; Moghbeli et al., 2019). There are various cell surface markers for detection and isolation of CSCs in BC (Amini, Fathi, Mobalegi, Sofimajidpour, & Ghadimi, 2014; Sedaghat et al., 2017). Doublecortin-like kinase 1 (DCLK1) (OMIM: 604742) as a serine/threonine protein kinase is a specific CSC marker in solid tumors associated with apoptosis, cell proliferation, and epithelial–mesenchymal transition (EMT) (Bailey et al., 2014; Fan, Qian, & Dai, 2017; Ikezono et al., 2017). It has been reported that there was increased DCLK1 expression among a sample of Iranian BC cases in comparison with normal margins. Moreover, the DCLK1 overexpression was correlated with higher stage, grade, poor prognosis, low survival rate, and tumor aggressiveness (Shafiei et al., 2019). BMI1 (OMIM: 164831) is belonged to the polycomb group (PcG) proteins which are transcriptional suppressors (Orlando, 2003). Moreover, BMI1 is also critical for the self-renewal of normal and cancer stem cells (Molofsky et al., 2003) which can be associated with its inhibitory function on INK4A/ARF locus. It has been reported that the BC tumor tissues had higher levels of BMI1 expression compared with normal margins. Moreover, there was a significant correlation between BMI1 expression and stage in which stage Ta tumors had significantly lower levels of BMI1 compared with tumors with stages T1 and T2 among a subpopulation of Iranian BC cases (Shafaroudi et al., 2008). Self-renewal and pluripotency are the main features of normal and CSCs during embryogenesis and tumorigenesis. OCT4 (OMIM: 164177), SOX2 (OMIM: 184429), and NANOG (OMIM: 607937) are important transcription factors during embryogenesis and differentiation (Chakravarthy et al., 2008; Lee, Kim, Rho, Han, & Kim, 2006; Pan & Thomson, 2007). BMI is also a transcriptional repressor associated with hematopoiesis and senescence (Leung et al., 2004). It has been observed that the majority of BC cases had NANOG and BMI overexpressions among a subpopulation of Iranian patients (Amini et al., 2014). OCT4 is an essential transcription factor for the self-renewal maintenance in pluripotent cells, somatic, and cancer stem cells. Therefore, OCT4 is acutely downregulated after the differentiation of stem cells (Pardo et al., 2010; van den Berg et al., 2010). It has been observed that there was
OCT4 overexpression in a sample of Iranian BC subjects (Atlasi, Mowl, Ziaee, & Bahrami, 2007). Another study has also been reported that there was a significant association among OCT4 expression, grade, and tumor stage among a group of Iranian BC patients. There was also a correlation between OCT4 expression and BC tumor aggressiveness (Hafei, Nouraei, Parvin, Ziaee, & Mowl, 2012). CD44 (OMIM: 107269) and aldehyde dehydrogenase 1 (ALDH1) (OMIM: 100640) have been used to detect urothelial carcinoma stem cells (Ho, Kurtova, & Chan, 2012; Immervoll, Hoem, Steffensen, Miletic, & Molven, 2011). ALDH1A1 belonged to the ALDH1 family and expressed in cancer stem cells (Ginestier, et al., 2007). CD44 is a hyaluronic acid receptor expressed in normal and cancer cells (Jaggupilli & Elkord, 2012). It has been reported that there were significant correlations between ALDH1A1 overexpression, age, high-grade and stage tumors, and tumor relapse among a sample of Iranian BC patients. Therefore, they introduced ALDH1A1 as a high-grade urothelial tumor marker and can be used for the targeted therapy against the CSCs. Moreover, more aggressive treatment was required for the ALDH1+/CD44+ tumors. (Keymoosi, Gheytanchi, Asgari, Shariftabrizi, & Madjd, 2014).

4 | NONCODING RNAS

Both of epigenetic and genetic changes are involved in tumorigenesis. In contrast to the genetic alterations, the epigenetic changes are reversible and regulate gene expression without DNA alterations. Epigenetic changes include DNA methylation, chromatin modifications, and noncoding RNA which are widely associated with different cellular processes. Therefore, aberrant epigenetic processes can result in neoplastic transformation. Micro-RNAs are noncoding RNAs involving in posttranscriptional regulation through binding with three untranslated regions (Soukop, et al., 2017). Regarding the high stability of miRNAs in biofluids they can be considered as valuable noninvasive markers (Mall, Rocke, Durbin-Johnson, & Weiss, 2013; Yun et al., 2012). The KLF4 (OMIM: 602253) and HOXD10 (OMIM: 142984) have been reported as direct targets of miR-10b (OMIM: 611576) in BC (Xiao et al., 2014). MiR-34b-3p (OMIM: 611374) can be associated with cell-cycle regulation through CCND2 (OMIM: 123833) (Tan, Zhang, Zhou, Liu, & Liang, 2019). The apoptosis and cell cycle can be regulated by miR-103/107 which promotes PI3K/AKT signaling through PTEN targeting (Yu et al., 2018). MiR-141 (OMIM: 612093) can be associated with negative regulation of cell growth and migration and apoptosis induction through targeting RUNX1 (OMIM: 151385) (Xu, Ge, Zhang, & Zhou, 2018). It has been observed that there were miR-10b (OMIM: 611576), miR-34b (OMIM: 611374), and miR-103 (OMIM: 613187) overexpressions and miR-141 (OMIM: 612093) underexpression in a subpopulation of Iranian BC cases in comparison with controls. Moreover, there was a correlation between grade and levels of miR-10b expression. The miR-141 and miR-34b expressions were also associated with addiction and metastasis, respectively. The low-grade patients had significant higher urine miR-10b in comparison with controls which can be introduced as a noninvasive marker for the early detection of BC (Nekooehseh et al., 2018). The miR-886-5p is considered as an oncomir through downregulation of BAX which results in apoptosis inhibition (Li et al., 2011). It has been observed that there was a significant miR-886-5p overexpression in high-grade in comparison with low-grade BC samples among a subpopulation of Iranian subjects. They also reported significant upregulation of miR-886-5p in invasive in comparison with noninvasive tumors (Khoshevisian et al., 2015). Another study has reported that there were increased expressions of miR200c (OMIM: 612092), miR-30b, and miR-141 levels in a subpopulation of Iranian BC tissues compared with normal margins. Moreover, miR-200c underexpression was correlated with poor prognosis and tumor progression to muscle (Mahdavinezhad, Mousavibahar, et al., 2015). MiR-21-5p (OMIM: 611020) induces the cell proliferation and migration through PTEN regulation (Folini et al., 2010). It is also involved in EMT process through activation of TGFβ and Hedgehog signaling pathways (Bonci et al., 2016). Moreover, miR-21-5p is a negative regulator of apoptosis by targeting FASL, BAX, and MARCKS (Li, Li, Sha, Sun, & Huang, 2009; Papagiannakopoulos, Shapiro, & Kosik, 2008). MiR-141-3p induces tumor cell proliferation through KLF-9 (OMIM: 602902) suppression (Li et al., 2017). Downregulation of miR-205-5p (OMIM: 613147) induces apoptosis and suppress cell proliferation through ZEB2 (OMIM: 605802) increased expression and ERBB3 (OMIM: 190151) decreased expression (Jiang et al., 2017). It has been shown that there were significant miR-21-5p, miR-141-3p, and miR-205-5p urinary overexpressions in a sample of Iranian BC cases, among them the miR-141-3p and miR-205-5p had highest and lowest levels of expression, respectively (Ghorbanmehr et al., 2019). Regarding metastasis to the muscles, BC is categorized into nonmuscle-invasive BC (NMIBC) and muscle-invasive BC (MIBC). MiR-200c induces BC invasion by targeting RECK (Cheng et al., 2016). The miR-141, miR-200c, and miR-30b overexpressions were observed in majority of a sample of Iranian BC patients. However, MIBC cases had lower levels of miR-30b, miR-141, and miR-200c expressions compared with NMIBC cases. There were a noticeable correlation between miR-141 underexpression and muscle invasion. Moreover, they showed a significant converse association between miR-141 expression and grade. Expressions of MiR-30b and miR-200c were also correlated with tumor size in which the tumors bigger than 10 cm had decreased expressions compared
with tumors smaller than that (Mahdavinezhad, Mousavi-Bahar, et al., 2015). MiR-205 is involved in EMT process through regulation of various genes such as ZEB1, VEGF-A (OMIM: 192240), and CDH1 (OMIM: 192090) (Kenney et al., 2011; Wiklund et al., 2011). MiR-99a (OMIM: 614509) is mainly introduced as a tumor suppressor and targets several important factors including m-TOR (OMIM: 601231), FGFR3 (OMIM: 134934), and IGF1 (OMIM: 147440) (Fischbach et al., 2015; Wu, Zhou, Pan, & Zhou, 2015).

It has been reported that there were miR-99a and miR-205 underexpressions in BC tissues compared with normal margins among a subpopulation of Iranian subjects. High-grade tumors with muscle invasion had higher levels of miR-99a expression compared with low-grade tumors which suggesting that as a marker of poor differentiated tumor cells (Gaji et al., 2017). MiR-21 has oncogenic roles through inhibition of several tumor suppressors including PTEN, TPM1 (OMIM: 191010), and MASPIN (OMIM: 154790) (Asangani et al., 2008; Zhu et al., 2008). The miR-21 can be upregulated by BMP-4 (OMIM: 112262) and TGF-β (OMIM: 190180) in vascular smooth muscle cells (Davis, Hilyard, Lagna, & Hata, 2008). TGF-β is involved in various processes such as cell growth, differentiation, and apoptosis (Keski-Oja, Koli, & von Melchner, 2004). It has been observed that there was significant TGF-β underexpression mainly in low-grade bladder tumors among a sample of Iranian cases. Moreover, the miR-21 expression was noticeably increased in high-grade tumors. There was significant correlation between the levels of miR21 and TGF-β expressions (Monfared et al., 2013). LncRNAs are nuclear or cytoplasmic noncoding RNAs involving in transcriptional or posttranscriptional gene regulation during cell proliferation and apoptosis (Enokida, Yoshino, Matsushita, & Nakagawa, 2016). Long intergenic noncoding RNAs (LincRNAs) are transcribed from intergenic regions which are associated with transcription and chromatin regulation (Vance & Ponting, 2014). LINC00152 as a lincRNA has important regulatory roles in various cellular processes such as cell cycle, apoptosis, and cell migration (Lv et al., 2013; Szafranski et al., 2013). LINC01082 (OMIM: 614978) can be also a transcriptional regulator of FOXP1 (OMIM: 601089). It has been reported that there were decreased levels of LINC00152 and LINC01082 expressions in majority of a sample of Iranian BC tissues compared with their normal margins. The tumor type was significantly correlated with decreased levels of LINC01082 expression. Moreover, they observed an association between age and LINC00152 underexpression (Ousati Ashtiani, Pourmand, Salami, Ayati, & Tavakkoly-Bazzaz, 2017).

Exosomes are natural nanoparticles containing proteins and RNAs which are involved in urothelial tumorigenesis through microenvironment modification (Beckham et al., 2014). Exosomes exert their roles through LncRNAs transfer between cells (Hewson & Morris, 2016). The MALAT1 (OMIM: 607924), LINC00958 (OMIM: 618335), LINC00355, and UCA1 (OMIM: 617500) are LncRNAs involving in regulation of cell proliferation, apoptosis, and migration (Han, Liu, Nie, Gui, & Cai, 2013; Seitz et al., 2017; Wang, Li, Xie, Zhao, & Chen, 2008). It has been observed that there were MALAT1, LINC00355, and UCA1-203 overexpressions in urinary exosomes of a sample of Iranian TCC cases compared with controls (Yazarlou, Modarressi, et al., 2018).

5 | CELL SIGNALING AND KINASES

The PI3K/AKT/mTOR signaling is associated with cell growth, cell migration, and angiogenesis (McCubrey et al., 2012). Phosphatidylinositol 3-kinases (PI3Ks) (OMIM: 601232) are lipid kinases producing PIP3 second messenger which induces cell growth and survival through AKT serine/threonine kinase (Cantley, 2002). The mTOR is also a serine/threonine kinase that is downstream mediator of PI3K/AKT pathway. It has been shown that the PIK3CA rs6443624 C>A and AKT1 rs2498801 A>G were protective variants of BC. They observed that the rs1130233 G>A and rs2295080 G>T variants of AKT1 (OMIM: 164730) and mTOR, respectively, increased the BC susceptibility among a subpopulation of Iranian patients (Bizhani et al., 2018). PI3K signaling pathway can be triggered by tyrosine kinase receptors (Knowles, Platt, Ross, & Hurst, 2009; Platt et al., 2009). PIK3CA mutational analysis was performed among a sample of Iranian BC patients which showed lower frequency of mutation in high-grade and advanced stage tumors (Ousati Ashitani, Mehrsai, Pourmand, & Pourmand, 2018).

HER-2/neu (OMIM: 164870) is a tyrosine kinase growth factor receptor. It has been observed that there was a correlation between higher grade of the TCC and HER-2/neu overexpression is a sample of Iranian patients (Jalali Nadoushan, Taheri, Jouian, & Zaeri, 2007). Centrosomal protein 55 (CEP55) (OMIM: 610000) is an oncogene involving in cytokinesis and regulation of PI3K/AKT signaling pathway (Jeffery, Sinha, Srihari, Kalimutho, & Khanna, 2016). Forkhead box protein M1 (FOXM1) (OMIM: 602341) regulates expression of various genes such as CDC25B (OMIM: 116949), CCNB (OMIM: 123836), pololike kinase 1 (PLK1) (OMIM: 602098), and CENP (Laoukili, Stahl, & Medema, 2007). PLK1 is also a serine/threonine kinase that induces cell proliferation through the cell-cycle checkpoint skipping leading to genetic instability (He et al., 2011; Park, Sohn, Park, Chung, & Kim, 2011). It has been shown that there were upregulations of CEP55, FOXM1, and PLK1 among a sample of Iranian BC tissues compared with their corresponding normal tissues (Seyedabadi et al., 2018). The fibroblast growth factor receptor (FGFR) as a tyrosine kinase receptor is one of the main regulators of cell-cycle progression, angiogenesis, and embryonic development. It has
been reported that there were FGFR1 (OMIM: 136350) and FGFR3 (OMIM: 134934) overexpressions in low-grade and all tumors, respectively, among a subpopulation of Iranian BC subjects (Ousati Ashtiani, Tavakkoly-Bazzaz, et al., 2017). The small G-protein signaling modulator 3 (SGSM3) (OMIM: 610440) is a GTPase involving in regulation of G-protein and Ras signaling (Yang, Sasaki, Minoshima, & Shimizu, 2007). It has been shown that the 4-bp ins/del genotype and ins allele of SGSM3 significantly increased the BC susceptibility among a subpopulation of Iranian patients (Hashemi et al., 2018). Sphingosine 1-phosphate (SIP) (OMIM: 601965) is a bioactive lysosphingolipid mediator that binds to S1PRn (a G-protein–coupled receptor) to regulate MAPKs. S1PR3 is involved in tumor cell migration and self-renewal. It has been reported that there were upregulation of S1PR1, S1PR2, and S1PR3 expressions in tumor tissues compared with normal margins in a subpopulation of Iranian BC patients. There were also correlations among S1PR1 overexpression, higher grades, and advanced stages (Palangi, Shakshsalim, Parvin, Bayat, & Allameh, 2019). S100 (OMIM: 617427) are calcium-binding proteins involving in cell proliferation, apoptosis, and inflammation. They are also the ligands for RAGE and Toll-like receptors which activates the MAPK, PI3K-AKT, and NF-κB signaling pathways. RAGE (OMIM: 605762) as a receptor is associated with tumor progression and diabetes (Sessa et al., 2014; Xie, Mendez, Mendez-Valenzuela, & Aguilar-Hernandez, 2013). It has been reported that there were increased expressions of S100A12 and RAGE in tumors in comparison with normal margins among a group of Iranian BC patients (Khorramdelazad et al., 2015). IGFBP-3 (OMIM: 146732) is the main carrier of IGF in blood stream. Moreover, IGFBP-3 affects cell signaling pathways and also binds with nuclear hormone receptors. It can be an oncogene or tumor suppressor based on tumor types. It has been observed that there were significant correlations between the A-202C (rs2854744) polymorphism of IGFBP-3 and BC susceptibility in a sample of Iranian patients. The CC genotype carriers had more aggressive bladder tumors and the C allele was correlated with higher BC risk compared with 202-A allele. Moreover, it was shown that the patient had significantly lower serum levels of IGF-1 (OMIM: 147440) and IGFBP-3 compared with controls (Safarinejad, Shafiei, & Safarinejad, 2011b). Tumor behavior and incidence rate can be associated with gender in which it has been observed that the aggressive tumors with poor prognosis are more frequent among females (Jemal, Siegel, Xu, & Ward, 2010; Miyamoto et al., 2012). This can be related to various factors such as different exposure to industrial chemicals, smoking, and hormonal differences (Bolenz, Lotan, Ashfaq, & Shariat, 2009; Mir et al., 2011). Sex steroid hormones function through their receptors in target cells (Miyamoto et al., 2012). It has been reported that there was a significant association between the AR expression and high-grade and stage tumors in a sample of Iranian BC cases. AR-positive cases had also significant higher rate of metastasis in comparison with AR-negative cases. Therefore, they introduced AR as a prognostic marker among Iranian UBC (Mashhadi et al., 2014). Smoking and exposure to aromatic amines and polycyclic hydrocarbons are considered as the main environmental risk factors of BC (Cohen, Shirai, & Steinbeck, 2000). Jun-terminal kinases (JNKs) are stress kinases activated following the ROS/RNS, heat, or osmotic shock which regulate cell cycle, DNA repair, and apoptosis through activation of several transcription factors such as c-JUN, ATF2 (OMIM: 123811), P53, and ELK-1 (OMIM: 311040) (Davis, 2000). Glutathione-S-transferases (GSTs) are involved in detoxification of xenobiotics, reactive oxygen species, and carcinogenic compounds (Schnakenberg, Breuer, Werdin, Dreikorn, & Schloot, 2000). Glutathione-S-transferase (GST) is a negative regulator switch for JNK. Low JNK activity is preserved through a GSTP1-JNK complex in nonstressed cells. ROS or drugs dissociate the GSTP1 (OMIM: 134660) from GSTP1-JNK complex which activates the JNK and its subsequent downstream events (Yin, Ivanov, Habelhah, Tew, & Ronai, 2000). It has been reported that there were significant correlations between GSTP1 Ile/Val or Val/Val genotypes and risk of BC in a group of Iranian patients. The GSTP1 Val/Val genotype was significantly correlated with grade and stage of tumor. Due to a synergistic relationship among GSTM1 (OMIM: 138350), GSTT1 (OMIM: 600436), and GSTP1, the presence of GSTM1 or GSTT1 nulls with GSTP1 Ile/Val or Val/Val genotypes significantly increased the BC susceptibility in this population. Moreover, the GSTP1 Ile/Val genotype was protective against high-grade and stage tumors (Safarinejad, Safarinejad, Shafiei, & Safarinejad, 2013).

6 | CANCER TESTIS ANTIGENS AND EMT

Cancer testis antigens (CTAs) are a group of proteins mainly expressed in normal testis and tumor tissues which are associated with cell proliferation and epithelial–mesenchymal transition (EMT) (Forghanifard et al., 2011; Yang, Huo, Liao, & Zhou, 2015). Exosomes are extracellular nanoparticles normally can be detected in biofluids. Exosome contents can be assessed to identify the pathophysiology of related tissues. Such contents may involve in pathogenesis of various disorders via modification of intercellular communication and microenvironment (Sun, Luo, Jiang, & Duan, 2018; Valadi et al., 2007). A group have been assessed the expression of CTAs in urinary exosomes of a subpopulation of Iranian BC cases compared with controls. It has been observed that there was MAGE-B4 (OMIM: 300152) overexpression in TCC patients in comparison with controls. Moreover, the TCC cases had also higher levels...
of exosomal NMP22 expression compared with BPH cases (Yazdari, Mowl, et al., 2018). EMT is a critical process during the tumor progression and metastasis. E-Cadherin as a cell adhesion protein is required for the normal integrity of epithelial cells and EMT process. Therefore, loss of CDH1 expression results in increased cell migration and invasiveness in solid tumors. It has been reported that there was a correlation between CDH1 expression and recurrent BC in a sample of Iranian patients (Khorrami et al., 2012). EMT is associated with various transcriptional repressors such as ZEB1 and Snail. TGF-β upregulates the ZEB1 expression via inhibition of miR-141, miR-200a, miR-200b, and miR-200c. It has been reported that the BC tissues had increased levels ZEB1 mRNA expression compared with control tissues among a sample of Iranian cases. Moreover, there was a correlation between TGF-β2 overexpression and muscle invasion (Mahdavinezhad et al., 2017).

Immune system is an important defense mechanism against the tumor cells (Smyth, Dunn, & Schreiber, 2006), however, the inflammation can be also an oncogenic mechanism through DNA damage and angiogenesis (Rakoff-Nahoum, 2006). IL-6 (OMIM: 147620) is an inflammatory cytokine which is involved in immune response, cell proliferation, and apoptosis (Kishimoto, 2005). It has a key role in neoplastic transformation through STAT3 (OMIM: 102582) (Iliopoulos, Jaeger, Hirsch, Bulyk, & Struhl, 2010). IL-12 (OMIM: 161,560) is another cytokine secreted by activated macrophages and dendritic cells (Colombo & Trinchieri, 2002) which inhibits tumorigenesis and angiogenesis (Sangro, Melero, Qian, & Prieto, 2005). It has been observed that there were significant correlations between IL-12 (3′UTR A>C) and IL-6 (-174 C>G) genotypes and increased BC susceptibility among a subpopulation of Iranian cases. The GC and GC+CC genotypes carriers at C-174G had higher risk of BC compared with GG genotype. In the case of IL-12, there was a significant correlation between BC risk and AC genotype of IL-12B (Ebadí et al., 2014). Chronic inflammation is one of the most important physiological processes involving in tumorigenesis. CD4+ T cells are categorized into T-helper 1 (Th1) and Th2 (Murphy & Reiner, 2002) that are involved in cell-mediated and humoral immune responses, respectively. Th17 cells are a class of CD4+ T cells producing IL-17A (OMIM: 603149) inflammatory cytokine which regulates the physiological state of various immune and nonimmune cells. IL-17 induces the inflammation through proinflammatory cytokines and metalloproteinases. It has been reported that there was increased IL-17A levels among a sample of Iranian BC cases compared with controls. Moreover, the advanced stage tumors had lower levels of IL-17A compared with early stages tumors (Doroudchi et al., 2013). The Th17 cell differentiation is regulated by various factors such as IL-21, TGF-β, and TNF-α (Nam et al., 2008; Shime et al., 2008). Th17 cells are associated with tumor regression through IL-17, VEGF, and TGF-β (Honarati, Neri, Cattini, & Facchini, 2006; Jeon et al., 2007). It has been shown that there were decreased serum levels of IL-17 and TGF-β in a subpopulation of Iranian BC cases compared with controls. Decreased serum levels of IL-17 and TGF-β were mainly in the early tumor stages which can be related to the inhibitory role of chemoradiotherapy on Th17 cells and TGF-β-producing tumor cells. They introduced IL-17 and TGF-β as targets for the immunotherapy of advanced stage BC (Baharlou, Ahmadi Vasmehjani, Dehghani, Ghobadifar, & Khoubi, 2014). Another study has been observed that there were increased and decreased levels of IL-17 and TGF-β, respectively, in a sample of Iranian BC subjects. The IL-17 upregulation was observed in BC with early stage tumors. They concluded that the IL-17 probably decreased TGF-β expressions in early stage of tumor progression (Baharlou et al., 2015).

In present review we summarized all of the reported genes until now among Iranian BC patients. To clarify the genetic and molecular biology of BC for the first time among Iranians, we categorized all of the significant reported genes based on their cell and molecular functions. Interestingly, we observed that the noncoding RNAs and epigenome are the main molecular processes associated with BC progression among Iranians. This review paves the way for determination of a population-based panel of genetic markers for the early detection of BC among Iranians.

None.

Majid Mojarrad was involved in search strategy and drafting. Meysam Moghbeli designed the project and also was involved in edition and drafting. All authors read and approved the final manuscript.

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