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# Bladder Cancer Biology

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## 1. Introduction

At present, bladder cancer (BCa) is worldwide the 9th most common tumor; in men it represents the 7th and in women 17th most common malignancy (Ploeg et al., 2009). In the European Union approximately 104,400 newly diagnosed BCa and 36,500 BCa-related deaths were estimated for the year 2006 (Ferlay et al., 2007). In the United States, approximately 70,530 new cases and 14,680 BCa-related deaths were expected for 2010 (Jemal et al., 2010). Men are three to four times more frequently affected than women (Ferlay et al., 2007; Jemal et al., 2010).

Detection of BCa is hampered due to lately emerging symptoms, such as hematuria, and the lack of specific tumor markers. Treatment options, particularly for the advanced disease, appear currently insufficient, leading together with the BCa-inherent high recurrence and progression rates to the relatively high BCa-related mortality (Ferlay et al., 2007). For the development of more specific and efficient diagnostic tools and therapeutic approaches a profound understanding of the onset and course of this disease is indispensable.

Molecular alterations that presumably lead to malignant transformation of the bladder urothelium belong to specified pathways involved in regulation of cellular homeostasis. As consequence of genetic and epigenetic alterations as well as of changes in subsequent regulatory mechanisms several major cellular processes are influenced in a manner that results in tumor development and progression. Regulation of the cell cycle, cell death and cell growth belong to these processes as well as the control of signal transduction and gene regulation. Particularly important for tumor cell spread and metastasis are changes in the regulation of interactions with stromal cells and extracellular components, of tumor cell migration and invasion and of angiogenesis (Mitra & Cote, 2009).

Interestingly, numerous associations between risk factors for the development of BCa and the affected cellular processes were identified (Mitra & Cote, 2009). For tobacco smoking or the occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and aniline dyes − the major environmental risk factors that contribute to BCa genesis − strong associations with alterations in cell cycle regulation have been reported (Bosetti et al., 2007; Golka et al., 2004; Mitra & Cote, 2009; Strope & Montie, 2008). Other factors such as use of hair dyes, several noxious substances and drugs, dietary components and urological pathologies influence with more or less evidence the control of cell cycle and the regulation of gene expression or signal transduction (Golka et al., 2004; Kelsh et al., 2008; Michaud, 2007; Mitra & Cote, 2009; Shiff et al., 2009).

Not only environmental risk factors determine the risk of BCa development, but also strong correlations with a genetic predisposition or polymorphisms in detoxification or repair genes leading to alterations in gene expression and regulation have been described (Bellmunt et al., 2007; Dong et al., 2008; Franekova et al., 2008; Garcia-Closas et al., 2006; Horikawa et al., 2008a; Kellen et al., 2007; Mitra & Cote, 2009; Sanderson et al., 2007).
Several genome-wide association studies revealed the association of different single nucleotide polymorphisms (SNPs) with an altered risk of BCa. Strong associations of SNPs on the chromosomes 3q28, 4p16.3, 8q24.21 and 8q24.3 with the risk of BCa development were observed (Kiemeney et al., 2008, 2010; Rothman et al., 2010; X. Wu et al., 2009). Rothman *et al*. identified also new chromosomal regions on 2q37.1, 19q12 and 22q13.1, which are related to the susceptibility for BCa (Rothman et al., 2010).

## 2. Different clinical behavior due to varying genetic & molecular pathways

Clinical behavior and outcome of superficial, non muscle-invasive BCa doubtless differ from muscle-invasive BCa what is the result of varying molecular pathways characteristic for each subtype [Fig.1]. The more frequently diagnosed non muscle-invasive BCa comprise papillary Ta tumors confined to the mucosa and T1 tumors spread into submucosal layers of the bladder. In dependence on tumor grade, stage and size, the presence of concomitant *carcinoma in situ* (*CIS*), the occurrence of multifocal lesions and the prior recurrence rate the risk of recurrence of non muscle-invasive Ta/T1 BCa and the risk of progression to muscle-invasive BCa differ considerably (Babjuk et al., 2011; Sylvester et al., 2006). In principle, flat *CIS* lesions also belong to the group of non muscle-invasive BCa but are associated with a higher aggressiveness due to a completely different tumor biological behavior rather resembling muscle-invasive BCa (Kitamura & Tsukamoto, 2006; Pashos et al., 2002).
It appears meaningful to regard the different types of non muscle-invasive BCa separately due to dissimilar phenotype-specific alterations in molecular and cellular pathways, which are also reflected by the varying clinical behavior. Ta tumors, which account for approximately 70% of non muscle-invasive BCa, bear a relatively high risk of local recurrence but rarely become muscle-invasive BCa (Kitamura & Tsukamoto, 2006; Pashos et al., 2002; Van Rhijn et al., 2009; Wu, 2005). The remaining non-muscle invasive BCa consist of 20% T1 tumors and about 10% primary *CIS* (Kitamura & Tsukamoto, 2006; Van Rhijn et al., 2009). Particularly, high grade T1 tumors (previously T1G3) have an increased propensity to progress compared to low grade T1 and Ta tumors (Emiliozzi et al., 2008; Kitamura & Tsukamoto, 2006). In contrast, *CIS* lesions are rather characterized by molecular alterations that are also observed in muscle-invasive BCa. Therefore, a high risk of progression of these *CIS* tumors seems to be implicated and leads to a poor outcome similar to that of muscle-invasive BCa (Knowles, 2008; Wu, 2005).
In low-grade papillary tumors a constitutively activated receptor tyrosine kinase/RAS pathway in consequence of activating mutations in the genes FGFR3 (*fibroblast growth factor receptor 3*) or HRAS (*Harvey rat sarcoma viral oncogene homolog*) was described (Jebar et al., 2005; Knowles, 2008; Wu, 2005). The rate of FGFR3 mutations of about 70% in Ta and in low-grade tumors is much higher than in invasive BCa with a rate of 10-20% (Bakkar et al., 2003; Billerey et al., 2001; Rieger-Christ et al., 2003; Serizawa et al., 2011).
Activating HRAS mutations are detected with an estimated overall frequency of 10-15% without a clear association with tumor grade or stage (Jebar et al., 2005; Knowles, 2008; Kompier et al., 2010a; Oxford & Theodorescu, 2003; Serizawa et al., 2011). Interestingly,

mutations in FGFR3 and in RAS genes are mutually exclusive events and therefore suggested to represent alternative means to activate the MAPK (*mitogen-activated protein kinase*) pathway resulting in the same phenotype (Jebar et al., 2005; Kompier et al., 2010a).
Furthermore, deletions of chromosome 9 belong to the most common genetic alterations in Ta tumors with a frequency of 36-66% (Knowles, 2008). Several putative tumor suppressor genes (TSG) located on this chromosome are affected by such deletions in combination with loss of heterozygosity (LOH) events, mutations or promoter hypermethylation (Knowles, 2008). Amongst others, the CDKN2A locus on 9p21 encoding the TSG $p16^{INK4A}$ and $p14^{ARF}$ is altered as well as PTCH1 (9q22.3), DBC1 (9q32-33) and TSC1 (9q34) located on the long arm of chromosome 9 (Aboulkassim et al., 2003; Berggren et al., 2003; Cairns et al., 1995; Chapman et al., 2005; Knowles, 2003, 2008; Lopez-Beltran et al., 2008; S.V. Williams et al., 2002; Williamson et al., 1995). LOH events in these chromosomal regions are associated with a high tumor grade and an elevated risk of recurrence of Ta and T1 tumors (Simoneau et al., 2000).
In principle, T1 tumors belong to the group of non-muscle-invasive BCa but obviously differ in their clinical behavior from Ta tumors since they show a higher potential for invasive growth and risk to progression. Nevertheless, dedifferentiation reflected by the tumor grade is a crucial factor for the determination of the phenotype resulting from differing molecular alterations (Kitamura & Tsukamoto, 2006). High-grade Ta tumors (TaG3) display a FGFR3 mutation frequency of 34% ranging between that of TaG1 (58-82%) and T1G3 tumors (17%) paralleling the phenotype and clinical behavior (Hernandez et al., 2005; Herr, 2000; Junker et al., 2008; Kitamura & Tsukamoto, 2006; Van Oers et al., 2007). Additionally, a high rate of homozygous deletions of the CDKN2A/INK4A gene, which was associated with an increased relative risk of recurrence, was observed in high-grade Ta tumors (Orlow et al., 1999).
Deletions or promoter hypermethylation of the CDKN2A/INK4A gene affect the expression of its gene products $p14^{ARF}$ and $p16^{INK4A}$ finally leading to deregulation in the p53 and RB1 (*retinoblastoma 1*) pathways. Alterations in these pathways are in fact molecular characteristics for *CIS* lesions and muscle-invasive BCa but can also be found in papillary tumors progressed to an invasive stage (Kitamura & Tsukamoto, 2006; Mitra & Cote, 2009; Orlow et al., 1999). Inactivation of p53 in muscle-invasive BCa is predominantly the consequence of allelic loss and mutations in this gene or of the homozygous deletion of its regulator $p14^{ARF}$ (Mitra & Cote, 2009). Disturbed expression or uninhibited hyperphosphorylation of the tumor suppressor RB1 result in its inactivation (Mitra & Cote, 2009). Simultaneous dysfunction of p53 and RB1, the two central regulators of the cell cycle and apoptosis, is observed in more than 50% of high grade T1 tumors and in the majority of muscle-invasive BCa (Kitamura & Tsukamoto, 2006; Knowles, 2008). Furthermore, two other alterations affecting the p53 pathway are characteristic for muscle-invasive BCa: the lack of $p21^{Waf1}$, the *cyclin-dependent kinase inhibitor 1A* (CDKN1A), and overexpression of the p53-regulator MDM2 (*Mdm2 p53 binding protein homolog (mouse)*) (Mitra & Cote, 2009).
Muscle-invasive BCa display a high number and variety of chromosomal alterations such as loss of 5q, 6q, 8p, 9p, 9q, 10q, 11p, 11q, 17p and Y or gains of 1q, 3q, 5p, 6p, 7p, 8q, 17q, 20p and 20q (Blaveri et al., 2005; Heidenblad et al., 2008; Knowles, 2008; Richter et al., 1998; Simon et al., 2000).
The frequency of specific genomic alterations increases with tumor stage and is associated with a worse outcome (Blaveri et al., 2005; Richter et al., 1998). Several genes putatively

relevant for tumor proliferation and progression are located in these altered chromosomal regions such as the transcription factors E2F3 and SOX4 on 6p22 or the supposed oncogene YWHAZ (14-3-3-zeta) on 8q22 (Heidenblad et al., 2008). Interestingly, amplification of 6p22 containing E2F3, which is involved in cell cycle regulation, and the frequently occurring homozygous deletions of CDKN2A and CDKN2B on 9p21 exist mutually exclusive indicating that they possibly play complementary roles (Feber et al., 2004; Heidenblad et al., 2008; Hurst et al., 2008; Oeggerli et al., 2004, 2006; Olsson et al., 2007).

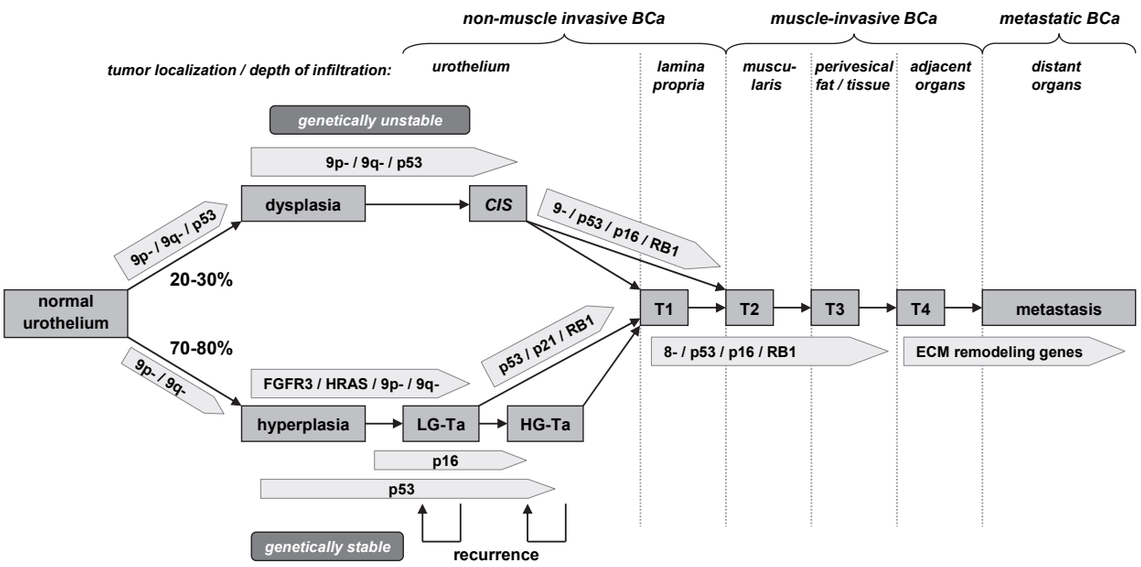


Fig. 1. Molecular pathways of BCa development and progression
Non-muscle invasive and muscle-invasive BCa fundamentally differ in their geno- and phenotypes. Varying genetic aberrations as well as the occurrence of p53 mutations in the normal urothelium are of crucial importance, which route of tumor progression will be followed. *Carcinoma in situ* (*CIS*) or muscle-invasive BCa, which may emerge from dysplasia of the urothelium, possess generally a high risk of progression. Papillary, non-muscle invasive Ta tumors, which are characterized by a high risk of recurrence and a lower risk of progression, rather develop from hyperplasia of the urothelium.
Abbreviations: 9p- / 9q- – loss of the short / long arm of chromosome 9, BCa – bladder cancer, *CIS* – *Carcinoma in situ*, ECM – extracellular matrix, HG-Ta – high grade Ta tumor, LG-Ta – low grade Ta tumor, T1 to T4 – tumor stages 1 to 4.

During progression and metastasis profound changes of regulatory networks involving the extracellular matrix (ECM), cell adhesion and migration, attraction of blood vessels and neovascularization occur, which characterize advanced tumor stages (Mitra & Cote, 2009). These processes comprise alterations in the regulation of cadherins, which are responsible for epithelial cell-cell adhesion, and *matrix metalloproteinases* (MMPs), which play an important role in the ECM-degradation as prerequisite for tumor cell migration (Mitra & Cote, 2009; Slaton et al., 2004; Wallard et al., 2006). Angiogenesis is driven by angiogenic factors such as the *vascular endothelial growth factor* (VEGF), one of the key factors responsible for tumor progression (Crew, 1999a).

## 3. Alterations in cell cycle regulation

Correct course of cell cycle is controlled by the p53 and RB1 pathways that are tightly linked with each other and influence regulation of apoptosis, signal transduction and gene expression [Fig.2]. The TSG p53, the central regulator of these processes, is located on chromosome 17p13.1, a region that is affected by allelic loss more frequently in BCa of higher stage and grade (Knowles, 2008; Olumi et al., 1990). Parallel to the loss of one 17p allele, frequently occurring mutations lead to the inactivation of the tumor suppressor p53 (Cordon-Cardo et al., 1994; Dalbagni et al., 1993; Sidransky et al., 1991). Mutated p53 becomes resistant to degradation and due to this longer stability detectable in the nucleus by immunohistochemistry (Dalbagni et al., 1993; Esrig et al., 1993). Such mutations were observed with a high frequency in BCa of higher stage and grade (Dalbagni et al., 1993; Esrig et al., 1993; Fujimoto et al., 1992; Puzio-Kuter et al., 2009; Serizawa et al., 2011; Sidransky et al., 1991). Therefore, the assessment of the nuclear immunoreactivity of altered p53 facilitates prognostic conclusions (Esrig et al., 1993; Kuczyk et al., 1995; Sarkis et al., 1993, 1995; Serth et al., 1995). Particularly for invasive, but still organ-confined BCa without metastasis (T1-2b N0 M0) and also for advanced BCa p53 is of prognostic importance with regard to the prediction of recurrence and cancer-specific mortality after radical cystectomy (Shariat et al., 2009a, 2009b). Nevertheless, nuclear accumulation and mutations of p53 provide differing contribution to the prediction of the outcome. Mutations and altered protein stability of p53 lead to worst prognosis compared to patients with one of these events and to patients with wild-type p53 and unchanged protein stability, who showed a more favorable outcome (George et al., 2007).

Interestingly, a study on BCa patients without evidence of distant metastases suggested that tumors harboring p53 mutations are more susceptible to adjuvant chemotherapy containing DNA-damaging agents such as e.g. cisplatin and doxorubicin (Cote et al., 1997). Possibly, these chemotherapeutics induce apoptosis in p53-mutated cells by uncoupling of the S and M cell cycle phases (Waldman et al., 1996). These observations built the basis for a large international multicenter clinical trial dealing with the assessment of response rates of high-risk patients with organ-confined invasive BCa to a chemotherapy containing DNA-damaging agents (Mitra et al., 2007). However, first data analysis did not confirm the predictive value of p53 immunohistochemistry (Stadler, 2009).

Wild-type p53 controls cell cycle progression at G1-S transition by transcriptional activation of $p21^{WAF1}$ (CDKN1A), a cyclin-dependent kinase inhibitor (CDKI) that additionally can be regulated by p53-independent mechanisms (El-Deiry et al., 1993; Michieli et al., 1994; Parker et al., 1995; Stein et al., 1998). As potent CDKI, $p21^{Waf1}$ inhibits the activity of cyclin-CDK2 or -CDK4 complexes, and thus functions as a regulator of cell cycle progression at G1 (Mitra et al., 2007). Loss or under-expression of $p21^{Waf1}$ appears to have impact on tumor progression and consequently on the outcome of the patients (Stein et al., 1998). Patients with wild-type p53 and $p21^{Waf1}$ positivity had the best prognosis whereas patients with altered p53 and maintained $p21^{Waf1}$ expression displayed worse outcome and patients with altered p53 and lack of $p21^{Waf1}$ showed the highest rate of recurrence and worst survival (Stein et al., 1998).

MDM2, located on chromosome 12q14.3-q15, is another component involved in the regulatory network of p53 and an indispensable factor for the feedback control of p53 stability. Transcription of MDM2 is induced by p53. In the form of an autoregulatory loop, MDM2 can build a complex with p53 and transports it to the proteasome for degradation (Mitra & Cote, 2009; Wu et al., 1993, 2005).

Degraded p53 in turn causes reduction in MDM2 levels, but this can be bypassed by MDM2 gene amplification, which is observed approximately in 5% of the BCa with an increased frequency in tumors of higher stage and grade (Simon et al., 2002). Additionally, MDM2 overexpression is a common event in BCa in strong association with p53 nuclear immunoreactivity (Lianes et al., 1994; Lu et al., 2002; Pfister et al., 1999, 2000). A combined assessment of alterations of p53, $p21^{Waf1}$ and MDM2 revealed that patients with mutant p53 and/or p53 nuclear overexpression, loss of $p21^{Waf1}$ and MDM2 nuclear overexpression exhibited the worst outcome (Lu et al., 2002). Furthermore, a specific SNP at nucleotide position 309 in the MDM2 promoter region was evaluated for prognostic and predictive purposes. It can predict a poor outcome particularly in conjunction with the mutation and SNP status of p53 (Horikawa et al., 2008b; Sanchez-Carbayo et al., 2007; Shinohara et al., 2009).

The chromosomal region 9q21, which is frequently lost in non-muscle invasive and in muscle-invasive BCa, harbors the gene locus CDKN2A (*cyclin-dependent kinase inhibitor 2A*) whose transcription results in two different splice variants, $p14^{ARF}$ and $p16^{INK4A}$ (Knowles, 2008; Quelle et al., 1995; S.G. Williams & Stein, 2004). Normally, $p14^{ARF}$ is induced by the transcription factor E2F and can inhibit transcription of MDM2 thereby blocking the MDM2-induced p53 degradation (S.G. Williams & Stein, 2004). Thus, $p14^{ARF}$ builds a link between the p53 and the RB1 pathways. The expression of the splice variant $p14^{ARF}$ is predominantly reduced by homozygous deletions and also by promoter hypermethylation in BCa (Chang et al., 2003; Dominguez et al., 2003; Kawamoto et al., 2006; W.J. Kim & Quan, 2005).

The gene product of the other splice variant, $p16^{INK4A}$, normally functions as CDKI by blocking the cyclin D-CDK4/6-mediated phosphorylation of the RB1 protein thereby maintaining it in its active hypophosphorylated state and preventing exit from the G1 phase (Quelle et al., 1995; Serrano et al., 1993). In a study on BCa of all stages and grades homozygous deletion of $p16^{INK4A}$ was observed in a lower frequency than of $p14^{ARF}$ (Chang et al., 2003). In another study on non-muscle invasive BCa a higher risk of recurrence was found for homozygous deletion of the CDKN2A gene where loss of both splice variants $p14^{ARF}$ and $p16^{INK4A}$ correlated with clinicopathological parameters of a worse prognosis due to the potential deregulation of both the p53 and RB1 pathways (Orlow et al., 1999).

Additionally, hypermethylation in the promoter region of $p16^{INK4A}$ was reported for BCa in a range of 6-60% (Chang et al., 2003; Chapman et al., 2005; Dominguez et al., 2003; Kawamoto et al., 2006; W.J. Kim & Quan, 2005; Orlow et al., 1999). Loss of $p16^{INK4A}$ protein expression in T1 tumors correlated significantly with a reduced progression-free survival and was an independent predictor of tumor progression (Kruger et al., 2005). In another study, aberrant $p16^{INK4A}$ protein expression was found to be an adverse prognostic factor only in T3-T4 tumors whereas abnormal immunoreactivity of p53 and $p16^{INK4A}$ was identified as an independent predictor of reduced survival for all muscle-invasive BCa (Korkolopoulou et al., 2001).

Concluding data on BCa, homozygous deletions in the CDKN2A gene were not associated with tumor stage or grade supporting the hypothesis that chromosomal alteration of 9p21 is an early event in bladder carcinogenesis (Berggren et al., 2003). Nevertheless, aberrant methylation of $p14^{ARF}$ and $p16^{INK4A}$ occurs more frequently in muscle-invasive than in non-muscle invasive BCa and seems to be associated with adverse clincopathological parameters as well as with a poor outcome (Dominguez et al., 2003; Kawamoto et al., 2006).

The CDKN2B gene located adjacent to CDKN2A on 9p21 encodes the CDKI $p15^{INK4B}$, which inhibits cyclin D1-CDK4/6 complexes similar to $p16^{INK4A}$ (Orlow et al., 1995). In contrast to $p16^{INK4A}$ no association was observed between the expression and promoter methylation status of $p15^{INK4B}$ whereas the rate of chromosomal alterations was comparable (M.W. Chan et al., 2002; Gonzalez-Zulueta et al., 1995; Le Frere-Belda et al., 2004; Orlow et al., 1995). Decreased $p15^{INK4B}$ mRNA expression was only observed in non-muscle invasive BCa; in muscle invasive BCa $p15^{INK4B}$ expression varied widely (Le Frere-Belda et al., 2001). The authors concluded that decreased $p15^{INK4B}$ expression might be an important step in early neoplastic transformation of the urothelium and could be caused by other mechanisms than deletion or promoter hypermethylation (Le Frere-Belda et al., 2001).

The potential TSG $p27^{Kip1}$ (CDKN1B) is located on chromosome 12p13.1-p12 and belongs to the Kip1 family of CDKIs. It inhibits cyclin D-CDK4/6 and cyclin E/A-CDK2 complexes consequently preventing RB1 hyperphosphorylation (Coats et al., 1996; Polyak et al., 1994). The prognostic value of $p27^{Kip1}$ was analyzed in several immunohistochemistry studies on non-muscle and muscle-invasive BCa which revealed that this factor is preferentially expressed in early stage BCa (Franke et al., 2000; Korkolopoulou et al., 2000; Rabbani et al., 2007). In non-muscle invasive BCa expression of $p27^{Kip1}$ decreased significantly with increasing grade and a significant correlation between low $p27^{Kip1}$ expression and shorter disease-free survival and overall survival was observed, facts that support the hypothesis that loss of $p27^{Kip1}$ confers a selective growth advantage to tumor cells (Kamai et al., 2001; Korkolopoulou et al., 2000; Migaldi et al., 2000; Sgambato et al., 1999). However, some studies on non-muscle invasive and/or muscle-invasive BCa did not reveal a significant association between the loss of $p27^{Kip1}$ and outcome (Doganay et al., 2003; Franke et al., 2000; Kuczyk et al., 1999), whereas other reports showed that a decreased expression of $p27^{Kip1}$ significantly correlated with worse prognosis (Kamai et al., 2001; Rabbani & Cordon-Cardo, 2000).

Another central pathway influencing cell cycle progression is the regulatory network around the nuclear phosphoprotein RB1, a TSG located on chromosome 13q14 (Cairns et al., 1991; Mitra et al., 2007; Takahashi et al., 1991; S.G. Williams & Stein, 2004). RB1 in its physiological active, hypophosphorylated form inhibits cell cycle progression at the G1-S checkpoint by sequestering transcription factors of the E2F family (Chellappan et al., 1991; Fung et al., 1987; Hiebert et al., 1992; Mihara et al., 1989). Hyperphosphorylation of RB1 abolishes its cell cycle-inhibitory activity by the release of E2F transcription factors leading to transcription of genes involved in DNA synthesis and progression through mitosis (Degregori et al., 1995; Hernando et al., 2004; Mitra et al., 2007). RB1 becomes hyperphosphorylated by different cyclin-CDK complexes, such as cyclin D1-CDK4/6 and cyclin E-CDK2, which in turn can be inhibited by specific CDKIs, such as $p16^{INK4A}$, $p21^{Waf1}$ and $p27^{Kip1}$. The phosphorylation-mediated inactivation of RB1 can be the consequence of the already described loss of different CDKIs (Mitra et al., 2007).

In addition, mutations and LOH events in the RB1 gene can also lead to loss of RB1 expression and consequently to unregulated cellular proliferation (Miyamoto et al., 1995; Wada et al., 2000; Xu et al., 1993). Therefore, both aberrant RB1 down-regulation and dominance of the hyperphosphorylated inactive RB1 can be associated with tumor progression (Cote et al., 1998). For BCa, the proportion of RB1 alterations due to loss or inactivation was reported to increase with tumor stage and grade (Cairns et al., 1991; Ishikawa et al., 1991; Wada et al., 2000; Xu et al., 1993).

Particularly muscle-invasive, advanced BCa with an altered RB1 expression had a more aggressive behavior reflected by significantly decreased survival (Cordon-Cardo et al., 1992; Cote et al., 1998; Logothetis et al., 1992).
Regarding both p53 and RB1 − the key players of cell cycle regulation − as well as the other components of this regulatory network, a combined analysis of multiple factors seems to be reasonable. Therefore, a multitude of comprehensive immunohistochemical analyses of different cell cycle regulators such as p53, RB1, MDM2, cyclin D1 and E, $p14^{ARF}$, $p16^{INK4A}$, $p21^{Waf1}$, $p27^{Kip1}$, Ki67 and PCNA (*proliferating cell nuclear antigen*) were performed on tissue specimens originating from non-muscle invasive and muscle-invasive BCa (Brunner et al., 2008; Cordon-Cardo et al., 1997; Cote et al., 1998; Grossman et al., 1998; Hitchings et al., 2004; Kamai et al., 2001; Korkolopoulou et al., 2000; Lu et al., 2002; Migaldi et al., 2000; Niehans et al., 1999; Pfister et al., 1999, 2000; Sarkar et al., 2000; Shariat et al., 2004, 2006, 2007a, 2007b, 2007c; 2007d, 2009a; Tut et al., 2001).

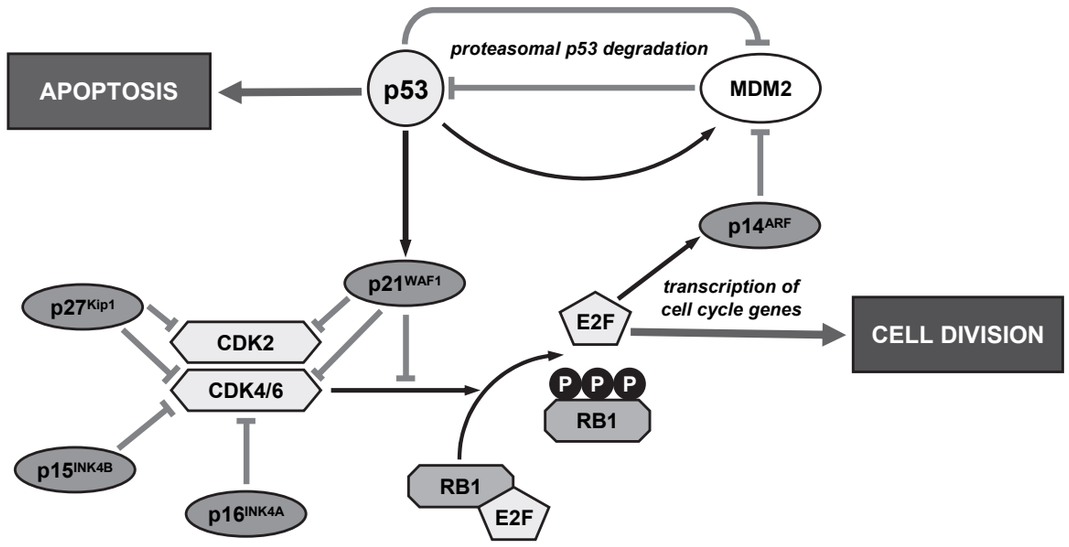


Fig. 2. Simplified illustration of the interactive network between the p53 & RB1 pathways
Transcription of MDM2 is induced by p53. In the form of an autoregulatory loop, MDM2 conveys p53 by ubiquitination to proteasomal degradation. Degraded p53 in turn causes reduction in MDM2 levels. Wild-type p53 can induce transcription of the CDKI $p21^{WAF1}$, which inhibits the activity of cyclin-CDK2 or -CDK4 complexes similar to the CDKI $p15^{INK4B}$, $p16^{INK4A}$ and $p27^{Kip1}$. When RB1 gets hyperphosphorylated by different cyclin-CDK complexes bound E2F transcription factors are released leading to the induction of cell cycle-promoting genes, but also to transcription of $p14^{ARF}$, which can inhibit MDM2.
Abbreviations: CDK – cyclin-dependent kinase, CDKI – cyclin-dependent kinase inhibitor, E2F – E2F transcription factors, MDM2 – *Mdm2 p53 binding protein homolog (mouse)*, $p14^{ARF}$ and p16 $^{INK4A}$ – splice variants of the *cyclin-dependent kinase inhibitor 2A* gene, $p15^{INK4B}$ – *cyclin-dependent kinase inhibitor 2B*, $p27^{Kip1}$ – *cyclin-dependent kinase inhibitor 1B*, RB1 – *retinoblastoma 1*.

The bottom line of most of these studies is that changes in gene expression, which can be caused by chromosomal alterations, promoter hypermethylation or altered regulation of

transcriptional induction, as well as alterations of stability, modification and activity of the different involved factors contribute to deregulation of the complex processes during cell cycle progression. The number of altered components correlates with the severity of dysfunction and deregulation finally leading to increased aggressiveness of the tumor and to worse prognosis. Most promising candidates, when analyzed in parallel with regard to prediction of the outcome of BCa patients, seem to be p53, RB1, $p16^{INK4A}$, $p21^{Waf1}$, $p27^{Kip1}$ and the proliferation marker Ki67. This prognostic information can support the stratification of the tumors according to their aggressiveness and the selection of adapted treatment options (Grossman et al., 1998).

## 4. Deregulation of cell death pathways

Course of development, cell differentiation and homeostasis is normally regulated by the tight control of cell death pathways [Fig.3]. This programmed cell death, the apoptosis, is usually induced by a variety of extra- and intracellular stimuli and is mediated by a complex arrangement of sensors, regulators and effectors whose interactions are frequently perturbed in tumor cells. Failure of apoptosis permits mutated cells to continue progression through the cell cycle, to accumulate mutations and to increase molecular deregulations. The resulting unrestricted propagation of active oncogenes and defective TSG finally leads to the uncontrolled proliferation and spread of these abnormal cells (Bryan et al., 2005a; Duggan et al., 2001; Mcknight et al., 2005). Defects and deregulation in the extrinsic and in the intrinsic apoptotic pathways contribute to development and progression of many tumors including BCa and are also the main reason for therapeutic failure. Particularly, defective p53 fails as detector of DNA damage and main inductor of apoptosis, when DNA repair was not achieved (Duggan et al., 2001).

The extrinsic apoptotic pathway is induced through the stimulation of cell surface death receptors by their corresponding ligands while the intrinsic pathway is switched on by the disruption of mitochondrial membranes. There is a cross-talk between both routes that finally lead to the cleavage of cellular proteins by caspases and subsequently to the degradation of the cells by gradual destruction of cellular components (Mcknight et al., 2005).

Transmembrane death receptors, such as FAS (CD95, APO-1), TNFR1, TRAILR1 or TRAILR2, belong to the *tumor necrosis factor* (TNF) receptor superfamily and contain an intracellular death domain. After binding of the respective ligands, such as FAS ligand, TNFα or TRAIL, extracellular death signals are transmitted via these domains by formation of a death-inducing signaling complex that activates the initiator caspases 8 and 10 (Mcknight et al., 2005; Mitra & Cote, 2009). Impairment of this processes was reported in BCa e.g. for FAS-mediated apoptosis that might be caused by mutation or decreased expression of FAS, which is associated with disease progression and poor outcome (Lee et al., 1999; Mcknight et al., 2005; Yamana et al., 2005). An alternative splice variant of FAS results in circulating soluble FAS that can capture the respective ligands and consequently prevent the normal death signal transduction. Soluble FAS, which was detected in serum and also in urine samples from BCa patients, could serve as predictor of recurrence and progression of BCa (Mizutani et al., 2001; Svatek et al., 2006).

The intrinsic or mitochondrial induced apoptotic pathway can be initiated by DNA damage or different cellular stress signals (Mcknight et al., 2005). The BCL2 (*B-cell CLL/lymphoma 2*)

family, which plays a crucial role in the intrinsic apoptotic pathway, consists of anti-apoptotic members, such as BCL2 and BCLXL (*BCL2-like 1*), as well as of pro-apoptotic members, such as BAX (*BCL2-associated X protein*), BID (*BH3 interacting domain death agonist*) and BAD (*BCL2-associated agonist of cell death*). BCL2 is an integral protein of the outer mitochondrial membrane that is involved in the control of ion channels, inhibition of cytochrome c release from the mitochondria or modulation of caspase activation (Mcknight et al., 2005; Mitra & Cote, 2009).

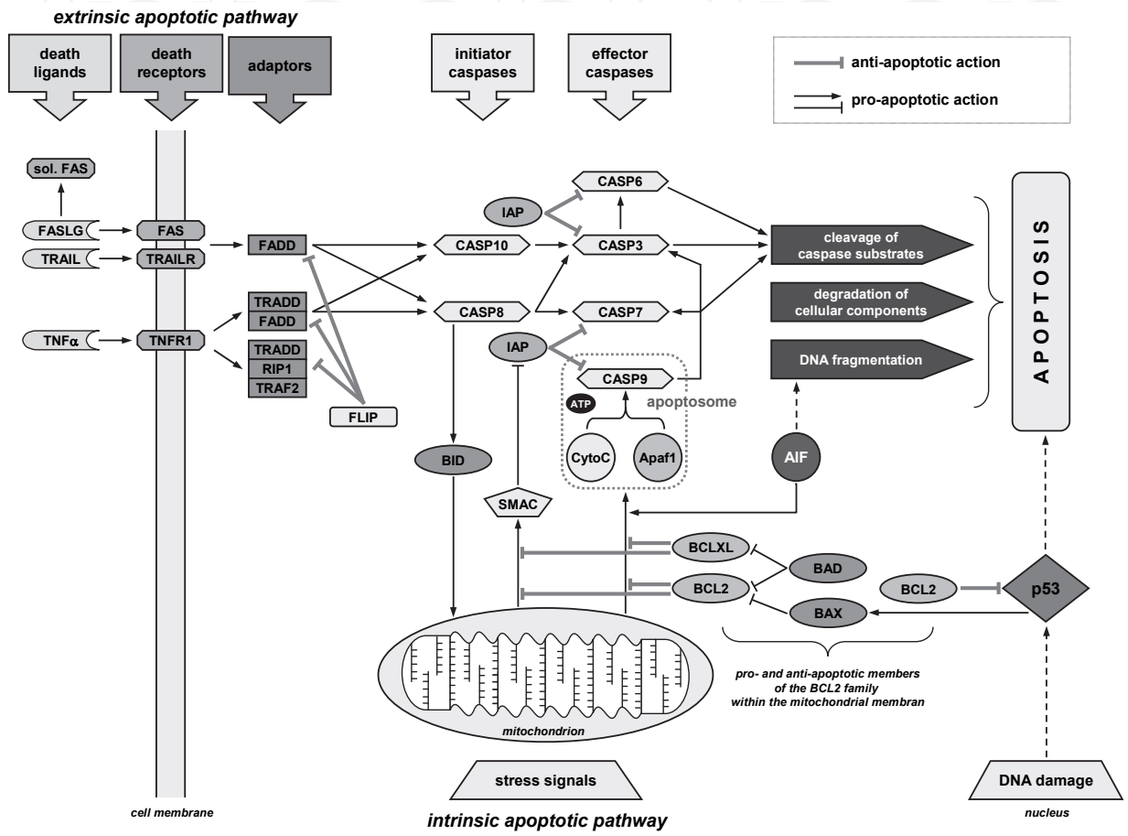


Fig. 3. Simplified illustration of the apoptotic cell death pathways
The extrinsic apoptotic pathway is induced through stimulation of cell surface death receptors by their corresponding ligands. The intrinsic mitochondrial route of apoptosis is initiated by DNA damage and cellular stress signals. Both pathways are interconnected and lead to the caspase-mediated cleavage of cellular proteins and consequently to the gradual degradation of further cellular components and cellular destruction.
Abbreviations: AIF – *apoptosis-inducing factor*, APAF1 – *apoptotic peptidase activating factor 1*, ATP – adenosine-5'-triphosphate, BAD – *BCL2-associated agonist of cell death*, BAX – *BCL2-associated X protein*, BCL2 – *B-cell CLL/lymphoma 2*, BCLXL – *BCL2-like 1*, BID – *BH3 interacting domain death agonist*, CASP – caspase, Cyto C – cytochrome c, DNA – deoxyribonucleic acid, FADD – *Fas-associated via death domain*, FAS – *Fas (TNF receptor superfamily, member 6)*, FASLG – *Fas ligand*, FLIP – *FLICE-inhibitory protein*, IAP – inhibitors of apoptosis, RIP1 – *receptor interacting protein 1*, SMAC – *second mitochondria-derived activator of caspase*, TNFR – *tumor necrosis factor receptor*, TRADD – *TNFR1-associated death domain protein*, TRAF2 – *TNF receptor-associated factor 2*, TRAIL – *TNF-related apoptosis inducing ligand*.

The export of cytochrome c into the cytoplasm and its binding to APAF1 (*apoptotic peptidase activating factor 1*) together with ATP induces the formation of apoptosomes that can cleave and activate pro-caspase 9. Subsequently, caspase 9 activates the effector caspases 3 and 7, which can be alternatively activated in the extrinsic pathway by the initiator caspases 8 and 10 as mentioned above. This caspase cascade finally commits the cell to apoptosis by gradual degradation of cellular proteins (Mcknight et al., 2005; Mitra & Cote, 2009).

BCL2 can block the apoptotic death and thereby trigger tumor recurrence and progression as well as mediate resistance to chemotherapy and radiation (Duggan et al., 2001). Different studies on non-muscle invasive and muscle-invasive BCa showed, that BCL2 was up-regulated in a varying number of the analyzed cases ranging from 41 to 63% (Cooke et al., 2000; Korkolopoulou et al., 2002; Liukkonen et al., 1997; Maluf et al., 2006; Ong et al., 2001). This BCL2 up-regulation correlated only partially with tumor stage and grade, but was frequently indicative for patients with poor prognosis after chemo- and/or radiotherapy (Cooke et al., 2000; Hussain et al., 2003; Ong et al., 2001; Pollack et al., 1997). Expression analyses of BCL2 together with other prognostic markers such as p53 and MDM2 revealed their usefulness as complementary predictors of survival of patients with non-muscle invasive and muscle-invasive BCa (Gonzalez-Campora et al., 2007; Maluf et al., 2006; Ong et al., 2001; Wolf et al., 2001).

Furthermore, the ratio between the anti-apoptotic factor BCL2 and the pro-apoptotic factor BAX seems to act as a cellular rheostat that might be predictive for a cell's response toward life or death after an apoptotic stimulus (Gazzaniga et al., 1996). BAX can be activated by BID that in turn can be induced by the initiator caspase 8. BAX forms a heterodimer with BCL2 and functions as an apoptotic activator by increasing the opening of the mitochondrial *voltage-dependent anion channel* (VDAC), which leads to the loss in membrane potential and the release of cytochrome c. The predominant expression of BCL2 over that of BAX correlated with a worse outcome and shorter time to relapse in low grade and non-muscle invasive BCa (Gazzaniga et al., 1996, 2003).

Apoptotic cell death can also be hampered by members of the IAP (inhibitor of apoptosis proteins) family that are also known as *baculoviral IAP repeat-containing* (BIRC) proteins. With regard to BCa, survivin (BIRC5) is the most interesting IAP since it can serve as diagnostic, prognostic and predictive marker (Margulis et al., 2008). Survivin inhibits apoptosis, promotes cell proliferation and enhances angiogenesis leading to its prominent role for tumor onset and progression in general and in particular for BCa (Margulis et al., 2008). For this tumor entity, high survivin expression at mRNA and protein levels is associated with advanced tumor grade and stage as well as with affection of lymph nodes (Karam et al., 2007a; I.J. Schultz et al., 2003; Shariat et al., 2007a; Swana et al., 1999; Weikert et al., 2005a). Survivin may serve either alone or together with other markers, such as p53, BCL2 and caspase 3, as a significant predictor of disease recurrence, progression and/or mortality after transurethral resection or radical cystectomy (Gonzalez et al., 2008; Karam et al., 2007a; 2007b; Ku et al., 2004; Shariat et al., 2007a). Response to chemo- and radiotherapy could also be estimated by the use of survivin as a predictive marker in BCa patients (Hausladen et al., 2003; Weiss et al., 2009).

For XIAP (*X-linked inhibitor of apoptosis* / BIRC4), which can directly inhibit the action of caspase 3, 7 and 9 and also interfere with the TNFR-associated cell death signaling, an up-regulation and association with an earlier recurrence was described in non-muscle invasive BCa (Dubrez-Daloz et al., 2008; Li et al., 2007).

Another IAP – cIAP2 (BIRC3) – that regulates apoptosis by binding to the TNFR-associated factors TRAF1 and TRAF2, has been shown to provoke chemoresistance when overexpressed in BCa cell lines (Jonsson et al., 2003). In expression analyses of livin (BIRC7) in tissue specimens from non-muscle invasive BCa only its anti-apoptotic isoform α was detected which was significantly associated with BCa relapse (Gazzaniga et al., 2003; Liu et al., 2009).

## 5. Immortalization of tumor cells – importance of the human telomerase

Activation of the human telomerase represents a very early event during the development of malignant tumors that leads to immortalization and as a consequence to the capability for unlimited division of tumor cells (Hiyama & Hiyama, 2002). Telomeres, the ends of eukaryotic chromosomes, normally get truncated during each cell division until they reach a critical length. This results in a severe impairment of the division capability leading to senescence of the cells (Harley, 1991). This senescence and the consequential cell death can be bypassed through activation of the telomerase ribonucleoprotein complex, since its catalytic subunit TERT (*telomerase reverse transcriptase*) supports the continuous prolongation of telomeres (Blackburn, 2005). Most of the differentiated somatic cells do not possess telomerase activity, whereas germline and stem cells as well as tumor cells frequently are telomerase-positive (Hiyama & Hiyama, 2002; N.W. Kim et al., 1994).

Several studies proved that TERT as well as the *telomerase RNA component* (TERC) represent essential subunits of the telomerase complex, but only TERT is specifically induced in cancer and functions as limiting factor of the enzymatic telomerase activity (Ito et al., 1998; Meyerson et al., 1997). Nevertheless, TERT protects the chromosomal ends also independently from its catalytic activity through its so-called capping function thereby providing tumor cells with further survival benefit (Blackburn, 2005; Blasco, 2002; S.W. Chan & Blackburn, 2002).

For most tumors it remains unclear whether TERT expression originates from telomerase-positive tumor stem cells or from the activation of the gene during tumorigenesis. A number of transcription factors, tumor suppressors, cell cycle inhibitors, hormones, cytokines and oncogenes have been implicated in the control of TERT expression but without providing a clear explanation for the tumor-specific TERT activity so far (Ducrest et al., 2002; Kyo et al., 2008).

Definitely, a tumor-specific activation of the telomerase complex is detectable in the majority of BCa. In contrast to telomerase-negative normal urothelium cells, > 90% of the analyzed BCa tissue specimens displayed a high expression and activity of telomerase (de Kok et al., 2000a; Heine et al., 1998; Hiyama & Hiyama, 2002; Ito et al., 1998; Lin et al., 1996; Muller, 2002). Therefore, the detection of TERT expression or the determination of telomerase activity in tissue or urine samples from patients suspected of having BCa is very useful for tumor detection (Alvarez & Lokeshwar, 2007; Glas et al., 2003; Muller, 2002; Weikert et al., 2005b). Possibly, quantitative determination of the TERT transcript levels in urine or bladder washings can support the prediction of recurrent BCa (Brems-Eskildsen et al., 2010; de Kok et al., 2000b).

## 6. Alterations in cell growth signaling

Cell growth signaling is transduced from the cell surface to the nucleus by different signaling cascades which can be altered and disturbed in tumor cells at different levels

leading to uncontrolled cell growth and proliferation [Fig.4]. In principle, peptide growth factors bind to their corresponding growth factor receptors on the cell surface leading to receptor activation and via several signal transduction events to the activation of downstream factors (RAS and RAF1). Through the subsequent activation of the MAPK pathway several transcription factors, such as MYC (*v-myc myelocytomatosis viral oncogene homolog (avian)*) or ELK1 (*ETS-like transcription factor 1*), are induced, which finally regulate the expression of growth-promoting genes. Transmission of extracellular growth signals can be altered in tumor cells at different levels of these cascades, e.g. by an abnormally increased supply of growth factors or by amplification, mutation or alternative up-regulation of the growth factor receptors leading to their constitutive, excessive and uncontrolled activity (Hanahan & Weinberg, 2000). Mutations or other regulatory alterations affecting downstream targets, such as members of the RAS family, can additionally provide tumor cells with an increased growth potential (Jebar et al., 2005; Knowles, 2008).

FGFR3, one of the four members of the FGFR family, is constitutively activated by different mutations, which are found in approximately 70% of low-grade Ta and to a much lower extent of 10-20% in muscle-invasive BCa (Bakkar et al., 2003; Billerey et al., 2001; Hernandez et al., 2006; Jebar et al., 2005; Junker et al., 2008; Knowles, 2008; Kompier et al., 2010a; Rieger-Christ et al., 2003; Van Oers et al., 2007; Van Rhijn et al., 2004). The most frequent mutations lead to amino acid substitutions to cysteine residues which can build covalent disulfide bonds mimicking dimerization and thereby activation of the receptor (Kompier et al., 2010b). Mutated FGFR3 correlates with favorable disease parameters and improved survival (Kompier et al., 2010b; Van Oers et al., 2007, 2009; Van Rhijn et al., 2001, 2004, 2010). In a recent multicenter study, the so called molecular grade, a combination of the FGFR3 mutation status and the proliferation marker Ki67, could improve the predictive accuracy of the EORTC (European Organisation for Research and Treatment of Cancer) risk scores for progression (Van Rhijn et al., 2010).

Mutated FGFR3 leads to the activation of the RAS-MAPK-pathway and consequently to an augmented transduction of growth signals. RAS mutations are found in BCa with an overall frequency of approximately 10-15% and do not depend on tumor grade or stage, (Jebar et al., 2005; Knowles, 2008; Kompier et al., 2010a; Oxford & Theodorescu, 2003; Serizawa et al., 2011). Such mutations occur in all three RAS genes (HRAS, NRAS and KRAS) whereby HRAS is affected most frequently (Jebar et al., 2005). Interestingly, simultaneous mutations in FGFR3 and RAS, both resulting in the activation of the same pathway, are very uncommon and rather occur mutually exclusive (Jebar et al., 2005). Thus, low grade and Ta tumors harbor mutations either of FGFR3 or HRAS in more than 80% of the cases reflecting the necessity of constitutive activation of the MAPK pathway for non muscle-invasive BCa (Jebar et al., 2005; Knowles, 2008).

Additionally, the up-regulation of FGFs can contribute to the pathogenesis of cancer (Bryan et al., 2005a). Levels of FGF1 (acidic FGF) in urine samples correlated with tumor stage (Chopin et al., 1993). An association with an increased tumor stage and early local recurrence was shown for the expression of FGF2 (basic FGF) (Bryan et al., 2005a; Gazzaniga et al., 1999).

The *epidermal growth factor* (EGF) receptor family comprising EGFR (ERBB1), ERBB2 (HER-2/neu), ERBB3 (HER3) and ERBB4 (HER4) represents another tyrosine kinase receptor family involved in growth signaling in BCa cells that can also transduce

extracelluar growth signals via the RAS-MAPK pathway or alternatively via the *phosphatidylinositol 3-kinase* (PIK3)-Akt pathway (Bryan et al., 2005a; Mitra & Cote, 2009). Expression at mRNA and protein level of all members of the EGFR family was observed in BCa specimens but with varying patterns of coexpression and differing prognostic impact, possibly depending on the size and composition of the patients cohorts and the detection techniques used in the different studies (Amsellem-Ouazana et al., 2006; Chow et al., 2001; Chow et al., 1997b; Forster et al., 2011; Junttila et al., 2003; Kassouf et al., 2008; Memon et al., 2006; Rotterud et al., 2005). Increased expression of EGFR and ERBB2 has been observed in a number of studies (Black & Dinney, 2008; Mitra & Cote, 2009). Many of these analyses revealed a correlation between increased levels of these two receptors and parameters of high risk tumors or of a poor prognosis for BCa patients (Black & Dinney, 2008; Mitra & Cote, 2009).

Several studies analyzed the BCa-related impact of growth factors activating EGFR, which comprise EGF, TGFα (*transforming growth factor alpha*), HB-EGF (*heparin-binding EGF-like growth factor*), epiregulin and others. Levels of TGFα in tissue samples and urine specimens from BCa patients correlated strongly with poor prognosis (Gazzaniga et al., 1998; Ravery et al., 1997; Thogersen et al., 2001; Turkeri et al., 1998). An association with tumor recurrence was also observed for EGF in BCa tissues, but not for urinary EGF (Chow et al., 1997a; Turkeri et al., 1998). Further studies revealed also an inverse correlation between the expression of epiregulin or nuclear HB-EGF and the survival of BCa patients (Adam et al., 2003; Kramer et al., 2007; Thogersen et al., 2001).

Another growth signaling pathway profoundly altered in many tumor entities including BCa is that of VEGF. This pathway is predominantly involved in the regulation of angiogenesis through the attraction and direction of blood vessels to the tumor by VEGF, which is secreted by tumor cells (Sato et al., 1998). Additionally, an autocrine function of VEGF in direct activation of the tumor cells themselves is assumed due to the observed up-regulation of different VEGF receptors such as FLT1 (VEGFR1) and KDR (VEGFR2 = FLK1) in BCa (Black & Dinney, 2008; Sato et al., 1998; Xia et al., 2006). An increased expression of KDR in BCa patients correlated with higher disease stage, muscle invasion and lymph node metastasis (Mitra et al., 2006; Xia et al., 2006).

PIK3CA (*phosphoinositide-3-kinase catalytic subunit alpha*) is part of the Akt signaling pathway and in this way also involved in the transformation of extracellular growth signals into an increased potential of cell proliferation and survival. PIK3CA mutations with an overall frequency of 13-25% seem to be a common event that occurs early in bladder carcinogenesis (Kompier et al., 2010a; Lopez-Knowles et al., 2006; Platt et al., 2009; Serizawa et al., 2011). A correlation with low stage and grade was observed in several studies (Lopez-Knowles et al., 2006; Serizawa et al., 2011). Interestingly, PIK3CA mutations were shown to be strongly associated with FGFR3 mutations possibly indicating cooperative oncogenic effects (Castillo-Martin et al., 2010; Kompier et al., 2010a; Lopez-Knowles et al., 2006; Serizawa et al., 2011). However, PIK3CA mutations showed no correlation with progression or disease-specific survival (Kompier et al., 2010a).

PTEN (*phosphatase and tensin homolog*), which is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and as such a negative regulator of the PIK3/Akt signaling pathway, acts by this way as a TSG. The PTEN gene located on 10q23.3 is frequently inactivated by chromosomal loss and mutations in a number of malignant tumors including BCa (Aveyard et al., 1999; Cairns et al., 1998; Knowles et al., 2009; Platt et al., 2009; Teng et al., 1997). The rate

of LOH events and allelic imbalances in a chromosomal region including the PTEN gene is with 23-32% in muscle-invasive BCa notably higher than in non-muscle invasive BCa (Aveyard et al., 1999; Cappellen et al., 1997; Knowles et al., 2009). Nevertheless, mutations in the retained PTEN allele or homozygous deletions do not occur very frequently indicating the existence of further mechanisms of PTEN inactivation (Aveyard et al., 1999; Cairns et al., 1998; Platt et al., 2009). A reduction in PTEN protein levels in BCa tissue specimens was observed in several studies and correlated with higher grade and/or higher stage (Harris et al., 2008; Platt et al., 2009; Puzio-Kuter et al., 2009; L. Schultz et al., 2010; Sun et al., 2011; Tsuruta et al., 2006). Interestingly, a reduced PTEN expression was related to poor outcome in BCa patients, particularly in those displaying alterations of p53 and PTEN (Puzio-Kuter et al., 2009).

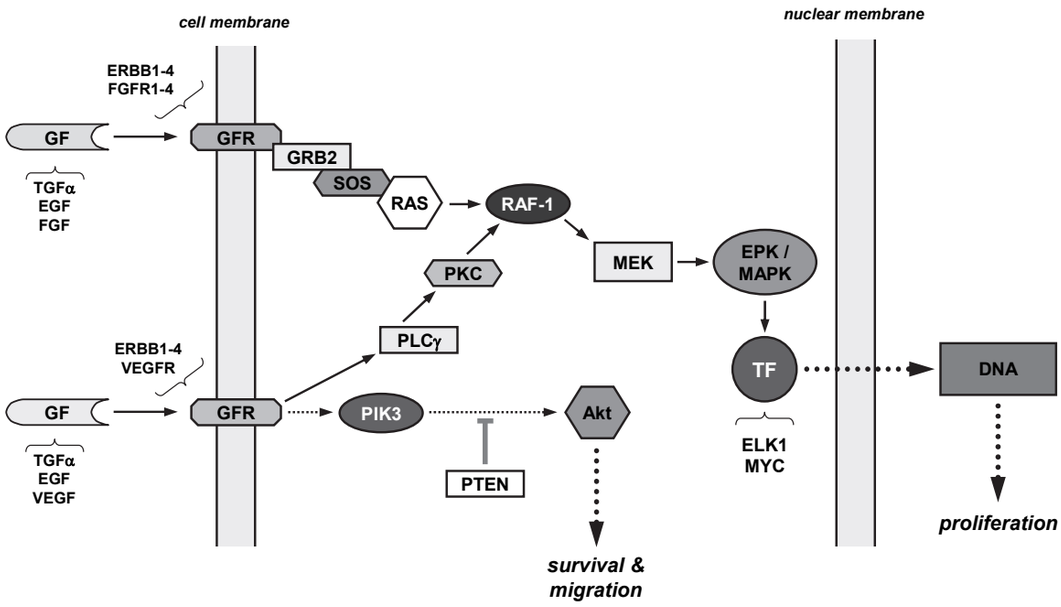


Fig. 4. Simplified illustration of the principles of growth factor signaling
Growth factors bind to their corresponding receptors at the cell surface thereby starting signaling cascades which transduce the signal through cytoplasmatic factors into the nucleus. There, genes supporting survival, proliferation and migration of the tumor cells are induced as final consequence. For BCa, the RAS/RAF/MEK/ERK- and the PIK3/AKT-pathways are of particular importance.
Abbreviations: Akt – *v-akt murine thymoma viral oncogene homolog 1*, DNA – deoxyribonucleic acid, EGF – *epidermal growth factor*, ELK – *member of ETS oncogene family*, ERBB – EGF receptor family member, ERK = MAPK1 – *mitogen-activated protein kinase 1*, FGF – *fibroblast growth factor*, FGFR – FGF receptor family member, GF – growth factor, GFR – growth factor receptor, GRB2 – *growth factor receptor-bound protein 2*, MEK – *mitogen-activated protein kinase kinase*, MYC – *v-myc myelocytomatosis viral oncogene homolog*, PIK3 – *phosphoinositide-3-kinase*, PKC – *protein kinase C*, PLCγ – *phospholipase C gamma*,
PTEN – *phosphatase and tensin homolog*, RAF-1 – *v-raf-1 murine leukemia viral oncogene homolog 1*, RAS – *rat sarcoma viral oncogene homolog*, SOS – *son of sevenless homolog*,
TF – transcription factor, VEGF – *vascular endothelial growth factor*, VEGFR – VEGF receptor family member.

The activation of the PIK3 pathway leads to transmission of extracellular growth signals via the phosphorylation of the serine-threonine protein kinase Akt (*v-akt murine thymoma viral oncogene homolog 1*) to the activation of several downstream signaling routes resulting in an increased proliferation, survival or migration of tumor cells (Wu et al., 2004). Elevated levels of phosphorylated Akt (pAkt) compared to normal bladder tissue were observed in different immunohistochemical studies on BCa tissue specimens (L. Schultz et al., 2010; Wu et al., 2004). Increased detection rates of pAkt correlated significantly with high-grade and advanced stage BCa as well as with a poor clinical outcome and survival (Sun et al., 2011). Furthermore, Askham *et al*. reported the detection of a transforming Akt mutation (G49A / E17K) in 2.7% of 184 analyzed BCa samples (Askham et al., 2010).

## 7. Tumor angiogenesis and metastasis

Angiogenesis comprises the recruitment and accelerated formation of new blood vessels from the surrounding vasculature. After proteolytic degradation of the adjacent ECM activated endothelial cells become able to migrate and invade as well as to maturate to coalescent, water-tight blood tubules (S.G. Williams & Stein, 2004). This essential physiologic process that occurs during development, reproduction and repair is tightly controlled by stimulatory and inhibitory regulators. During tumor genesis and progression this balance is disturbed by the up-regulation of angiogenic inducers and/or loss of anti-angiogenic factors which can be secreted by the tumor cells themselves, by neighboring tumor-associated stromal cells or by tumor-infiltrating inflammatory cells (S.G. Williams & Stein, 2004). Newly formed blood vessels provide the tumor cells with oxygen and nutrients, which is an essential prerequisite for rapid tumor growth and also for tumor cell spread during metastasis (Mitra & Cote, 2009). A high microvessel density (MVD) in the tumor as reflector of angiogenic processes is a strong predictor of a poor outcome of BCa patients (Bochner et al., 1995; Canoglu et al., 2004; Chaudhary et al., 1999; Dickinson et al., 1994; Hawke et al., 1998; Jaeger et al., 1995; Philp et al., 1996).

Hypoxia, which is frequently occurring in growing tumors, results in elevated levels of the hypoxia-inducible transcription factors HIF-1 and HIF-2. Stability of the HIF-1 subunit α is regulated by the cellular oxygen concentration via the inhibition of its oxygen-dependent degradation. HIF-1α (HIF1A) can induce transcription of VEGF which in turn stimulates tumor vascularization (Mitra & Cote, 2009). In BCa specimens, a significant positive correlation between HIF-1α, VEGF and MVD was observed (Chai et al., 2008; Theodoropoulos et al., 2004). Similar to MVD and VEGF, HIF-1α can serve as indicator of a high recurrence rate and short survival of patients with non-muscle invasive and muscle-invasive BCa (Chai et al., 2008; Palit et al., 2005; Theodoropoulos et al., 2004). Focused on non-muscle invasive BCa, HIF-1α overexpression combined with aberrant nuclear p53 accumulation seemed to indicate an aggressive phenotype with a high risk of progression (Theodoropoulos et al., 2005).

High mRNA expression of VEGF in non-muscle invasive BCa correlated with high recurrence and progression rates, particularly in combination with aberrant p53 staining (Crew et al., 1997). Elevated VEGF protein levels in urine samples from patients with non-muscle invasive BCa showed a significant association with tumor recurrence (Crew et al., 1999b).

Elevated VEGF serum levels were observed in BCa patients with high tumor grade and stage, with vascular invasion, *CIS* tumors or distant metastases and correlated with a shorter disease-free survival (Bernardini et al., 2001). Furthermore, VEGF expression and MVD in biopsy specimens taken prior to therapy were significant predictors of recurrence of muscle-invasive BCa after neoadjuvant chemotherapy and radical cystectomy (Inoue et al., 2000). Increased VEGF levels in tissue samples from patients with locally advanced BCa treated by radical cystectomy and chemotherapy (MVAC) were strongly related to poor disease-specific survival (Slaton et al., 2004).

*Thrombospondin-1* (TSP-1) is an ECM component glycoprotein that functions as potent inhibitor of angiogenesis. Expression analyses of this putative tumor suppressor in tissue specimens from patients with muscle-invasive BCa who underwent radical cystectomy revealed a significant association between low TSP-1 levels and increased recurrence rates as well as with a decreased overall survival (Grossfeld et al., 1997). In non-muscle invasive BCa a reduced perivascular TSP-1 staining served as independent predictor of progression to muscle-invasive or metastatic disease (Goddard et al., 2002). Furthermore, expression of *angiopoietin 2* (ANG-2), an angiogenic modulator that potentiates angiogenesis in presence of VEGF, was identified as a strong and independent predictor of tumor recurrence of non-muscle invasive BCa (Szarvas et al., 2008).

The scaffolding ECM serves to maintain endothelial cell function and its degradation is mediated amongst others by MMPs. Additionally, MMPs activate the basic and acidic FGF (FGF1 and FGF2) as well as the *scatter factor* (SF; identical to HGF = *hepatocyte growth factor*) – all regulators which promote migration and invasion of endothelial cells as well as of tumor cells thereby supporting angiogenesis and metastasis (Mitra & Cote, 2009). These factors are also stimulated by plasmin that is proteolytically generated by the *urokinase-type plasminogen activator* (uPA = PLAU = *plasminogen activator, urokinase*). uPA, which can be induced by VEGF, as well as its receptor uPAR (PLAUR= *plasminogen activator, urokinase receptor*) are also involved in ECM degradation, adhesion and migration of tumor cells (Mitra & Cote, 2009).

Determination of the FGF1 and FGF2 levels in urine samples of patients with BCa revealed their prognostic value as indicators of increased disease stage and high rates of local recurrence (Chopin et al., 1993; Gazzaniga et al., 1999; Gravas et al., 2004; Nguyen et al., 1993). SF/HGF levels in urine and serum samples were elevated in BCa patients and related particularly to higher tumor stages as well as to metastasis and worse survival (Gohji et al., 2000; Joseph et al., 1995; Rosen et al., 1997; Wang et al., 2007). The receptor of SF/HFG, the *met proto-oncogene* (MET), was also detected in BCa tissue specimens. Its up-regulation correlated with disease progression and poor long-term survival (Cheng et al., 2002, 2005; Joseph et al., 1995; Miyata et al., 2009).

A significant association between the expression of uPA and uPAR was observed in BCa tissues; both factors were higher in muscle-invasive than in non-muscle invasive BCa and correlated with a worse outcome (Champelovier et al., 2002; Hasui et al., 1994; Seddighzadeh et al., 2002). Elevated levels of uPA and uPAR were also detected in urine and plasma samples from BCa patients compared to controls without BCa (Casella et al., 2002; Shariat et al., 2003). Furthermore, increased preoperative uPA plasma levels in BCa patients were shown to be indicators of a poor outcome after radical cystectomy (Shariat et al., 2003).

Metastasis is initiated by the ability of the tumor to degrade the ECM and to invade the basement membrane followed by the invasion of tumor cells into blood and lymphatic

vessels, the path for tumor cell to spread into regional lymph nodes and secondary organs (Gontero et al., 2004; Mitra & Cote, 2009). Several key mediators are involved in metastatic spread such as cadherins which are located at adherens junctions and desmosomes between neighboring cells. Particularly, E-cadherin plays an important role in epithelial cell-cell contacts which is mediated by homodimerization and anchoring to the actin cytoskeleton via binding to catenins (Bryan et al., 2005b). In BCa patients, a reduced expression of E-cadherin was associated with an increased aggressiveness and a higher risk of tumor recurrence and progression as well as with a shorter survival (Bringuier et al., 1993; Byrne et al., 2001; Mahnken et al., 2005; Mhawech-Fauceglia et al., 2006; Nakopoulou et al., 2000; Popov et al., 2000). Immunohistochemical analyses of E-cadherin, α- and β-catenin revealed that loss of these factors can indicate a poor survival of BCa patients (Clairotte et al., 2006; Garcia Del Muro et al., 2000; Kashibuchi et al., 2007; Mialhe et al., 1997; Shimazui et al., 1996).

In addition, integrins are involved in the regulation of processes linked to tumor cell invasion and migration consequently leading to metastasis. Integrins are heterodimeric transmembrane glycoproteins on the surface of tumor cells that function as receptors of ECM proteins such as laminin and collagen. Thereby, integrins serve as molecular links between the ECM and the intracellular actin cytoskeleton and are in this way involved in the maintenance of normal tissue architecture (Gontero et al., 2004). Among the numerous members of the integrin family α6β4 integrin, which closely interacts with collagen VII and laminin thereby restricting cell migration, is one of the best studied integrins in BCa patients (Gontero et al., 2004). Altered expression of α6β4 integrin was observed in superficial BCa; in muscle-invasive BCa loss of α6β4 integrin and/or collagen VII or lack of their co-localization was reported (Liebert et al., 1994). BCa patients with weak α6β4 integrin immunoreactivity showed a better outcome than those with either no or strong expression (Grossman et al., 2000).

MMPs and members of the uPA system are proteases involved not only in invasion processes of endothelial cells, they are also key factors triggering the invasion of tumor cells by degradation of ECM and the basement membrane (Gontero et al., 2004). MMPs are frequently overexpressed and secreted in human tumors (Bryan et al., 2005b; Wallard et al., 2006). Additionally, members of the ADAM (*a disintegrin and metalloproteinase domain*) family have been implicated in cancer progression (Frohlich et al., 2006). An imbalance between MMPs and their natural counterparts, the *tissue inhibitors of metalloproteases* (TIMPs), which is frequently observed in tumors, is also assumed to support tumor cell invasion and metastasis (Gontero et al., 2004). TIMPs might be paradoxically up-regulated in response to the elevation of MMPs levels (Gontero et al., 2004).

For BCa, MMP-2 and MMP-9 are of particular prognostic importance since increase in their tissue levels correlated with higher tumor grade and/or stage (Davies et al., 1993; Kanayama et al., 1998; Papathoma et al., 2000). Overexpression of MMP-2 and MMP-9 in BCa tissues was associated with disease progression and poor survival (Durkan et al., 2003; Vasala et al., 2003). The ratio of the MMP-9 to E-cadherin levels in BCa tissue specimens was also useful for prediction of the disease-specific survival of patients with locally advanced BCa (Slaton et al., 2004).

Additionally, poor outcome was reported for BCa patients with high levels of TIMP-2 in tumor and/or stromal cells and for patients with increased tissue expression of MMP-2 and TIMP-2 or MMP-9 and TIMP-2 (Gakiopoulou et al., 2003; Grignon et al., 1996; Hara et al., 2001; Kanayama et al., 1998).

Higher recurrence rates and poor prognosis were observed in BCa patients with high serum levels of MMP-2, MMP-3 or with high ratios of the serum levels of MMP-2 to TIMP-2 (Gohji et al., 1996a, 1996b, 1998). MMP-1, MMP-2, MMP-9 and TIMP-1 were also detectable in urine samples from BCa patients and correlated with increasing grade and/or stage (Durkan et al., 2003; Durkan et al., 2001; Gerhards et al., 2001; Nutt et al., 1998, 2003; Sier et al., 2000). Urinary MMP-1 was associated with higher rates of disease progression and death from cancer (Durkan et al., 2001).

ADAM12, a disintegrin and metalloproteinase, that was shown to be up-regulated in BCa tissues in association with disease stage, could also be detected in urine samples, where it might serve as biomarker reflecting presence of BCa (Frohlich et al., 2006).

## 8. Conclusion

On the basis of specific genetic and molecular patterns two clearly distinguishable types of BCa can be defined, which differ in their phenotype and clinical behavior. They mainly diverge in the genetic stability and in the presence of alterations in the genes p53 and FGFR3. The knowledge of BCa-related genetic and molecular processes provides the basis for the development of new diagnostic and therapeutic approaches. Molecular-diagnostic assays can be designed for BCa subtypes, e.g. for low grade and low stage tumors, which are poorly detectable by the currently used techniques. Furthermore, new BCa subtype-selective therapeutics will provide more specific and effective treatment options leading to the reduction of tumor recurrence and progression. After successful implementation, both aspects will improve clinical outcome of BCa patients and save costs for diagnosis and therapy for this tumor type, which are huge compared to other tumor entities.

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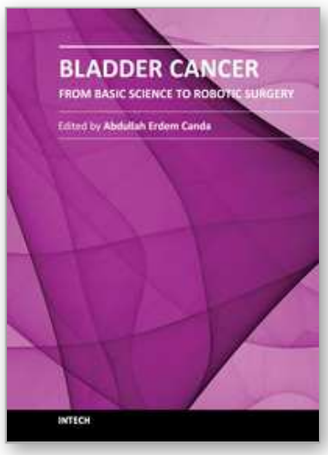


**Bladder Cancer - From Basic Science to Robotic Surgery**
Edited by Dr. Abdullah Canda

ISBN 978-953-307-839-7
Hard cover, 460 pages
**Publisher** InTech
**Published online** 01, February, 2012
**Published in print edition** February, 2012

This book is an invaluable source of knowledge on bladder cancer biology, epidemiology, biomarkers, prognostic factors, and clinical presentation and diagnosis. It is also rich with plenty of up-to-date information, in a well-organized and easy to use format, focusing on the treatment of bladder cancer including surgery, chemotherapy, radiation therapy, immunotherapy, and vaccine therapy. These chapters, written by the experts in their fields, include many interesting, demonstrative and colorful pictures, figures, illustrations and tables. Due to its practicality, this book is recommended reading to anyone interested in bladder cancer.

**How to reference**
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Susanne Fuessel, Doreen Kunze and Manfred P. Wirth (2012). Bladder Cancer Biology, Bladder Cancer - From Basic Science to Robotic Surgery, Dr. Abdullah Canda (Ed.), ISBN: 978-953-307-839-7, InTech, Available from: http://www.intechopen.com/books/bladder-cancer-from-basic-science-to-robotic-surgery/bladder-cancer-biology

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