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Original Article

Truncating *CDKN1A* mutations: an insight into the biology of urinary tract carcinomas?

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Abstract: A recent *in silico* study by Arnoff and El-Deiry found that urothelial carcinomas of the bladder and upper tract as well as chromophobe renal cell carcinoma are more likely than other malignancies to harbor alterations in the *CDKN1A* gene, encoding for the cyclin-dependent kinase inhibitor $p21^{Waf1}$, a major target of p53 regulatory pathways. Most of these mutations were truncating and thus presumably resulting in loss of $p21^{Waf1}$ function. Herein, we discuss the prognostic and therapeutic implications of these findings.

Keywords: CDKN1A, p21, urothelial carcinoma of the bladder, upper tract urothelial carcinoma, chromophobe renal cell carcinoma

In a recent *in silico* exploration of publicly available pancancer genomic datasets, Arnoff and El-Deiry [1] noted that urothelial carcinomas of the bladder (UCB) and upper tract (UTUC) as well as chromophobe renal cell carcinoma (chRCC) were more likely than other cancers to harbor alterations in the *CDKN1A* gene, which encodes for the cyclin-dependent kinase inhibitor $p21^{Waf1}$, a major target of p53 regulatory pathways [2]. Per the cBioPortal web-based open resource [3, 4], the frequency of *CDKN1A* alterations average ~10.6% in UCB, ~9.5% in UTUC, and ~4.6% in chRCC. The majority of mutations noted were truncating thus presumably resulting in loss of $p21^{Waf1}$ function. This *CDKN1A* propensity towards truncating alterations was not noted in other malignancies or in the *TP53* mutations that are often found in UCB, UTUC, and chRCC [1]. Of note, *CDKN1A* alterations are mutually exclusive with *TP53* in UCB and UTUC but this pattern is not observed in chRCC [3, 4].

The putative biological cause for the common predisposition for truncating *CDKN1A* mutations, as opposed to other alterations, in three urinary tract carcinomas (UCB, UTUC, and chRCC) remains to be determined. Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) mutational signatures are often found in UCB, and in subsets of UTUC and chRCC [5-7]. However, when comparing tumors harboring *CDKN1A* alterations with those that do not, no significant differences were noted in APOBEC pathway, homologous recombination pathway or most mismatch repair pathway genes [1]. Furthermore, whereas UCB tumors harboring *CDKN1A* alterations were enriched for alterations in genes such as *RB1*, *MUC16*, *HRNR*, *RAB44*, and *FLG* [1], this pattern was not found in neither UTUC nor chRCC [3, 4]. The high prevalence of truncating *RB1* mutations noted in UCB, lung adenocarcinoma and lung squamous cell carcinomas spurred the interesting hypothesis that the mutagenic effects of smoking may be linked to the RB1 dysregulation [1]. This may be supported by the low incidence of *RB1* alterations in chRCC, a malignancy with weak or no association with smoking [8]. On the other hand, however, although smoking is a major risk factor for UTUC [9], *RB1* mutations are rarely found in these tumors [10].

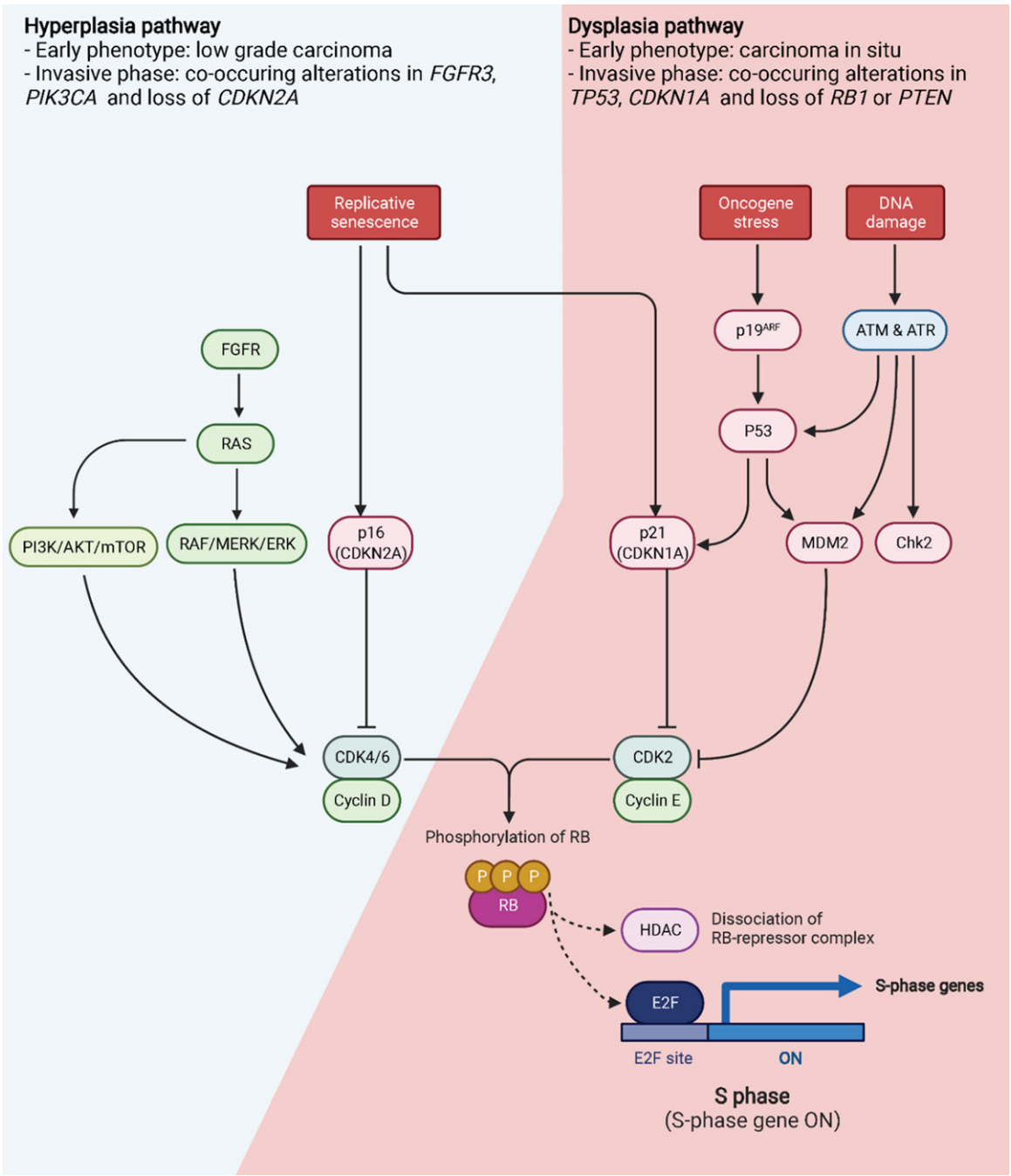

Figure 1. Proposed roles of various co-occurring genomic alterations, particularly cell-cycle regulation loss, in urothelial cancer development. Figure was created using biorender.com.

Approximately a third of patients with invasive UCB lose cell-cycle control in their tumors due to homozygous deletion (HD) of *CDKN2A* [11, 12], which is a well-established tumor-suppressor gene encoding p16 and $p14^{ARF}$. Furthermore, *CDKN2A* HD co-occurs with *FGFR3* and *PI3KCA* alterations but is mutually exclusive of *CDKN1A*, *RB1* and *TP53* alterations [13]. The two major pathways involved in the oncogenesis of UCB are the hyperplasia (FGFR/PI3KCa-driven) pathway in low-grade papillary non-muscle-invasive UCB and the dysplasia (TP53- and Rb1-driven) pathway in muscle-invasive UCB [14, 15]. The findings by Arnoff and El-Deiry [1] suggest that the cell cycle regulators p16 and p21 play distinctive roles in the hyperplasia and dysplasia pathways, respectively (**Figure 1**).

Despite its anatomical proximity to UTUC, chRCC has distinct histomorphological appearance and is treated very differently than either UCB and UTUC [16-20]. For example, in contrast to UCB and UTUC, chRCC is typically resistant to immune checkpoint therapies targeting the programmed cell death protein 1 (PD1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathways, and does not respond to cytotoxic chemotherapy agents, including DNA damage-inducing platinum salts [20]. Sarcomatoid dedifferentiation is noted in ~21% of metastatic chRCC cases and represents an unmet therapeutic need due to its aggressiveness and frequent resistance to all currently available systemic therapies [20, 21]. The observation by Arnoff and El-Deiry [1] that *CDKN1A* harbors truncating mutations in UCB, UTUC, and chRCC opens intriguing prognostic and therapeutic possibilities that should be functionally explored.

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Disclosure of conflict of interest

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