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Commentary

Loss of function mutations in *CDKN1A* are permissive for APOBEC3-induced mutagenesis in urothelial carcinoma

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Abstract: Mutagenic mechanisms that shape the genomic landscape and dysfunction of DNA repair converge to promote bladder tumorigenesis. A recent study by Arnoff and El-Deiry highlights the unique interactions between *CDKN1A* loss of function mutations, which play a key role in cell cycle regulation, modulating DNA repair, and inducing cell apoptosis and senescence, and APOBEC3-induced mutagenesis, the predominant contributor of mutations in urothelial carcinoma.

Keywords: CDKN1A, APOBEC3, mutagenesis, urothelial carcinoma

CDKN1A encodes for $p21^{Cip1/Waf1}$, a cyclin-dependent kinase inhibitor that could bind to and inhibit the activity of cyclin-dependent kinase 1/2 (CDK1/2) to halt cell cycle progression [1, 2]. Besides this, $p21^{Cip1/Waf1}$ plays a significant role in modulating DNA repair processes, regulating gene transcription, and inducing cell apoptosis and senescence [3]. These critical functions of $p21^{Cip1/Waf1}$ mediate its tumor-suppressive roles in tumorigenesis.

A recent study by Arnoff and El-Deiry [4] examined the potential mutagenic mechanisms that contribute to *CDKN1A* mutations and their functional impact on urothelial cancer cells. By analyzing whole-exome data from The Pan-Cancer Atlas (TCGA) project, the investigators found that *CDKN1A* alterations occur in up to 10.46% of patients with urothelial cancer. Interestingly, patients with lung cancer, a cancer type that shares tobacco smoking as a risk factor with urothelial cancer, have only a much lower 1% prevalence of the *CDKN1A* alterations. This suggests that, despite exposure to the same external mutagen, other internal mutagenic mechanisms are responsible for *CDKN1A* alterations in urothelial cancers. The majority (86%) of *CDKN1A* mutations in urothelial carcinoma patients are truncating loss of function mutations. Given the high prevalence of APOBEC3-associated mutational signatures in urothelial cancers [5, 6] and the APOBEC3 enzymes' ability to introduce nonsense mutations in viral genomes [7], the authors investigated whether *CDKN1A* nonsense mutations may result from APOBEC3-induced deamination. In addition to these truncating mutations, the authors also discovered that 16% of the copy number losses of *CDKN1A* in urothelial cancers are heterozygous events. The detailed mechanisms of these copy number losses are unknown. More evidence has recently emerged that APOBEC3-induced kataegis, a pattern of clustered mutations, is concentrated around genomic rearrangements [8, 9] and is associated with chromothripsis regions [10, 11] in several cancer types, implying that APOBEC3-induced mutagenesis is also involved in the genesis of structural variants. Since the single-strand DNA overhangs at DNA double-strand break sites are potential substrates for the APOBEC3 enzymes, APOBEC3 activity could interfere with DNA double-strand break repair. Impaired DNA double-strand break repair

would lead to the loss of heterozygosity [12]. Thus, APOBEC3 activity might contribute to the copy number loss of *CDKN1A* in urothelial cancer via impairing double-strand break repair.

Furthermore, Arnoff and El-Deiry found that urothelial cancers harboring *CKDN1A* mutations frequently co-occurred with alterations in DNA repair or cell cycle genes, including *RB1* and *RAB44*. As a critical cell cycle gene, $p21^{Cip1/Waf1}$ halts cell cycle progression at different phases by inhibiting the kinase activity of CDK-Cyclin complexes [3], allowing additional time for DNA repair. Moreover, $p21^{Cip1/Waf1}$ is critical for regulating DNA repair and activating apoptosis induced by overwhelming DNA damage [3, 13]. Thus, the loss of function of *CDKN1A* is permissive for the accumulation of mutations in the cancer genome. Interestingly, $p21^{Cip1/Waf1}$ mediates the E2F4 transcriptional complex's repression of APOBEC3B expression [14], a predominant mutagenic member of the APOBEC3 family. In conclusion, loss of function of *CDKN1A* potentially promotes the accumulation of APOBEC3-induced mutations via multiple mechanisms, ultimately contributing to the prevalence of these mutational signatures in urothelial cancers. The study also proposes a model in which environmental mutagens cooperate with other DNA repair pathways to promote carcinogenesis.

The investigators also found statistically significant enrichments in alterations in DNA repair genes, such as *MSH6*, *PMS1*, *BRCA1*, and *PALB2,* in tumors that also had *CDKN1A* mutations. These results suggest a potential connection between the loss of function of *CDKN1A* and the APOBEC3 activity in urothelial cancer, finally leading to the accumulation of the mutations in DNA repair genes. These results also indicate that urothelial cancers with the loss of function of *CDKN1A* could potentially harbor synthetic lethal vulnerabilities [15].

This important study adds to our knowledge of mutagenic mechanisms that shape the genomic landscape of urothelial cancers and highlights the unique interactions between *CDKN1A* loss of function mutations and APOBEC3-induced mutagenesis.

Disclosure of conflict of interest

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References

[1] El-Deiry WS, Tokino T, Velculescu VE, Levy DB, Parsons R, Trent JM, Lin D, Mercer WE, Kinzler KW and Vogelstein B. WAF1, a potential mediator of p53 tumor suppression. Cell 1993; 75: 817-825.

[2] El-Deiry WS, Harper JW, O'Connor PM, Velculescu VE, Canman CE, Jackman J, Pietenpol JA, Burrell M, Hill DE and Wang Y. WAF1/CIP1 is induced in p53-mediated G1 arrest and apoptosis. Cancer Res 1994; 54: 1169-1174.

[3] Abbas T and Dutta A. p21 in cancer: intricate networks and multiple activities. Nat Rev Cancer 2009; 9: 400-414.

[4] Arnoff TE and El-Deiry WS. CDKN1A/$p21^{WAF1}$, RB1, ARID1A, FLG, and HRNR mutation patterns provide insights into urinary tract environmental exposure carcinogenesis and potential treatment strategies. Am J Cancer Res 2021; 11: 5452-5471.

[5] Faltas BM, Prandi D, Tagawa ST, Molina AM, Nanus DM, Sternberg C, Rosenberg J, Mosquera JM, Robinson B, Elemento O, Sboner A, Beltran H, Demichelis F and Rubin MA. Clonal evolution of chemotherapy-resistant urothelial carcinoma. Nat Genet 2016; 48: 1490-1499.

[6] Alexandrov LB, Kim J, Haradhvala NJ, Huang MN, Tian Ng AW, Wu Y, Boot A, Covington KR, Gordenin DA, Bergstrom EN, Islam SMA, Lopez-Bigas N, Klimczak LJ, McPherson JR, Morganella S, Sabarinathan R, Wheeler DA, Mustonen V; PCAWG Mutational Signatures Working Group, Getz G, Rozen SG and Stratton MR; PCAWG Consortium. The repertoire of mutational signatures in human cancer. Nature 2020; 578: 94-101.

[7] Fan J, Ma G, Nosaka K, Tanabe J, Satou Y, Koito A, Wain-Hobson S, Vartanian JP and Matsuoka M. APOBEC3G generates nonsense mutations in human T-Cell leukemia virus type 1 proviral genomes *in vivo*. J Virol 2010; 84: 7278-7287.

[8] Davis CF, Ricketts CJ, Wang M, Yang L, Cherniack AD, Shen H, Buhay C, Kang H, Kim SC, Fahey CC, Hacker KE, Bhanot G, Gordenin DA, Chu A, Gunaratne PH, Biehl M, Seth S, Kaipparettu BA, Bristow CA, Donehower LA, Wallen EM, Smith AB, Tickoo SK, Tamboli P, Reuter V,

Schmidt LS, Hsieh JJ, Choueiri TK, Hakimi AA; The Cancer Genome Atlas Research Network, Chin L, Meyerson M, Kucherlapati R, Park WY, Robertson AG, Laird PW, Henske EP, Kwiatkowski DJ, Park PJ, Morgan M, Shuch B, Muzny D, Wheeler DA, Linehan WM, Gibbs RA, Rathmell WK and Creighton CJ. The somatic genomic landscape of chromophobe renal cell carcinoma. Cancer Cell 2014; 26: 319-330.

[9] Nik-Zainal S, Alexandrov LB, Wedge DC, Van Loo P, Greenman CD, Raine K, Jones D, Hinton J, Marshall J, Stebbings LA, Menzies A, Martin S, Leung K, Chen L, Leroy C, Ramakrishna M, Rance R, Lau KW, Mudie LJ, Varela I, McBride DJ, Bignell GR, Cooke SL, Shlien A, Gamble J, Whitmore I, Maddison M, Tarpey PS, Davies HR, Papaemmanuil E, Stephens PJ, McLaren S, Butler AP, Teague JW, Jönsson G, Garber JE, Silver D, Miron P, Fatima A, Boyault S, Langerød A, Tutt A, Martens JW, Aparicio SA, Borg Å, Salomon AV, Thomas G, Børresen-Dale AL, Richardson AL, Neuberger MS, Futreal PA, Campbell PJ and Stratton MR; Breast Cancer Working Group of the International Cancer Genome Consortium. Mutational processes molding the genomes of 21 breast cancers. Cell 2012; 149: 979-993.

[10] Cortés-Ciriano I, Lee JJ, Xi R, Jain D, Jung YL, Yang L, Gordenin D, Klimczak LJ, Zhang CZ and Pellman DS; PCAWG Structural Variation Working Group, Park PJ; PCAWG Consortium. Comprehensive analysis of chromothripsis in 2,658 human cancers using whole-genome sequencing. Nat Genet 2020; 52: 331-341.

[11] Maciejowski J, Chatzipli A, Dananberg A, Chu K, Toufektchan E, Klimczak LJ, Gordenin DA, Campbell PJ and de Lange T. APOBEC3-dependent kataegis and TREX1-driven chromothripsis during telomere crisis. Nat Genet 2020; 52: 884-890.

[12] Moynahan ME and Jasin M. Loss of heterozygosity induced by a chromosomal double-strand break. Proc Natl Acad Sci U S A 1997; 94: 8988-8993.

[13] Moldovan GL, Pfander B and Jentsch S. PCNA, the maestro of the replication fork. Cell 2007; 129: 665-679.

[14] Periyasamy M, Singh AK, Gemma C, Kranjec C, Farzan R, Leach DA, Navaratnam N, Pálinkás HL, Vértessy BG, Fenton TR, Doorbar J, Fuller-Pace F, Meek DW, Coombes RC, Buluwela L and Ali S. p53 controls expression of the DNA deaminase APOBEC3B to limit its potential mutagenic activity in cancer cells. Nucleic Acids Res 2017; 45: 11056-11069.

[15] Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, Mortimer P, Swaisland H, Lau A, O'Connor MJ, Ashworth A, Carmichael J, Kaye SB, Schellens JH and de Bono JS. Inhibition of Poly(ADP-Ribose) polymerase in tumors from *brca* mutation carriers. N Engl J Med 2009; 361: 123-134.