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Analysis

From infection to tumor: genetic evidence of viral antibody immune response' role in urologic cancer development

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Abstract

Background Urologic tumors are among the most common malignancies worldwide, and the association between chronic infections and the risk of developing these tumors has garnered significant attention. However, traditional observational studies are prone to confounding factors, making it challenging to establish a clear causal relationship.

Method This study employs a two-sample bidirectional Mendelian randomization analysis, utilizing genetic data on antibody levels and urologic tumors obtained from GWAS databases. The inverse variance weighted (IVW) method was used to estimate causal relationships, while MR-Egger and MR-PRESSO methods were applied for sensitivity analyses to assess horizontal pleiotropy and heterogeneity.

Result The results showed that antibody levels associated with various viral infections were significantly correlated with the risk of developing urologic tumors. For example, antibodies related to cytomegalovirus IgG and Epstein-Barr virus (EBV) were found to have complex associations with the risk of prostate cancer, bladder cancer, and testicular cancer. Some antibodies, such as those related to Varicella zoster virus, were associated with a reduced risk of clear cell renal carcinoma. Additionally, sensitivity analyses suggested the potential presence of horizontal pleiotropy in bladder and testicular cancers.

Conclusion Through Mendelian randomization analysis, we revealed a potential causal relationship between antibody immune responses and urologic tumors. These findings provide new evidence for the role of chronic infections in the pathogenesis of urologic tumors, suggesting that prevention and treatment strategies targeting related pathogens, such as vaccination and antiviral therapies, could offer new avenues for the prevention and management of urologic cancers.

Keywords Mendelian randomization · Urologic tumors · Chronic infection · Antibody-mediated immune response · Pathogen

1 Introduction

Globally, cancer incidence and mortality have increased rapidly with the aging and growth of the population [1, 2]. Research findings indicate that in the year 2022, newly diagnosed cases of urinary system tumors comprised approximately 13.15% of the overall total, with a mortality rate representing approximately 8.17% of the total cases [1]. The

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predominant urologic malignancies include prostate cancer, bladder cancer, renal cancer, renal pelvis cancer, and testicular cancer [3]. According to recent research findings, the year 2022 witnessed an estimated global mortality of 396,792 individuals due to prostate cancer, 220,349 due to bladder cancer, 155,702 due to renal cancer, and 9,056 due to testicular cancer [1]. In malignant renal tumors, renal cell carcinoma (RCC) accounts for approximately 90%, with clear cell renal cell carcinoma (ccRCC) comprising about 70% to 80% of RCC cases [4, 5]. In contrast to other types of cancer, urinary system cancers typically exhibit a slow progression and a high likelihood of being curable when diagnosed and treated promptly [6]. Nevertheless, the initial stage of urinary system tumors are often asymptomatic. Screening methods such as cystoscopy, needle biopsy, and imaging studies are constrained in their application for widespread screening due to their invasive nature, expense, and exposure to ionizing radiation [7]. Consequently, the identification of novel targets for large-scale screening and prevention of urinary system tumors is imperative.

Recent researches have implicated infectious agents in the pathogenesis of various non-communicable diseases, including tumors, autoimmune disorders, and Alzheimer's disease [8–10]. Furthermore, infectious pathogens play a significant role in the etiology of various cancers. However, due to its anatomical and physiological characteristics, the urinary system is particularly susceptible to infections [11]. Chronic infections and inflammation can lead to cellular damage, increased cell turnover, and the formation of a tumor-promoting microenvironment [12, 13]. For instance, Schistosoma haematobium infection is a well-known risk factor for bladder cancer in endemic regions [14]. Kryst P. et al. have identified a high prevalence of Epstein-Barr virus (EBV) and adenovirus (ADV) infections in individuals with renal cancer, correlating with an increased incidence of high-grade renal cell carcinoma (RCC) [15]. Furthermore, investigations have demonstrated that compromised antiviral defense mechanisms contribute significantly to the etiology of cervical cancer, bladder cancer, and head and neck cancer [16]. However, the roles of other pathogens, such as bacteria and viruses, in urinary system tumors remain unclear and warrant further investigation.

Hence, an examination of the antibody immune response in the context of urinary system tumors may offer novel perspectives and approaches for the prevention and treatment of such tumors. Regrettably, the existing research predominantly relies on retrospective data, resulting in inadequate evidential support. However, traditional observational studies may be limited in drawing valid conclusions due to confounding factors or reverse causation [17]. Thus, a novel approach is required to investigate the causal relationship between antibody immune responses and urologic malignances. Mendelian randomization (MR) approach, an epidemiological technique, has been extensively used in causal inference to mitigate confounding and bias resulting from limited sample sizes and cross-sectional designs.

We use a two-sample bidirectional MR approach, which considers genetic variations as instrumental variables (IVs), utilizing summary data from Genome-Wide Association Studies(GWAS) to explore the potential causal link between antibody immune response and 5 urologic malignances including prostate cancer, bladder cancer, ccRCC, renal pelvis cancer, and testicular cancer.

2 Methods

2.1 Study design

We defined antibody level used to indicate the antibody immune response as exposure and five urologic malignances as outcome. In reverse MR, urologic tumors serve as the exposure, and antibody levels are evaluated as the outcome. To reduce potential bias of the study, it is essential to follow the three core assumptions of the MR approach: (1) the instrumental variable (IV) must be significantly associated with the exposure; (2) the IV should affect the outcome exclusively through the exposure; and (3) the IV must not be connected to the outcome through confounding factors [18]. A summary of the study design is shown in the Fig. 1.

2.2 Data source

We collected GWAS summary data for 5 urologic malignances from the FinnGen Biobank R10 [19].These malignances were diagnosed based on ICD-O-3 criteria, with controls excluding all cancer cases. Additional details can be found in Supplementary Tables.

We obtained the data of antibody levels through the NHGRI-EBI GWAS catalog (https://www.ebi.ac.uk/gwas/publications/33204752/) from GCST90006884—GCST90006929.

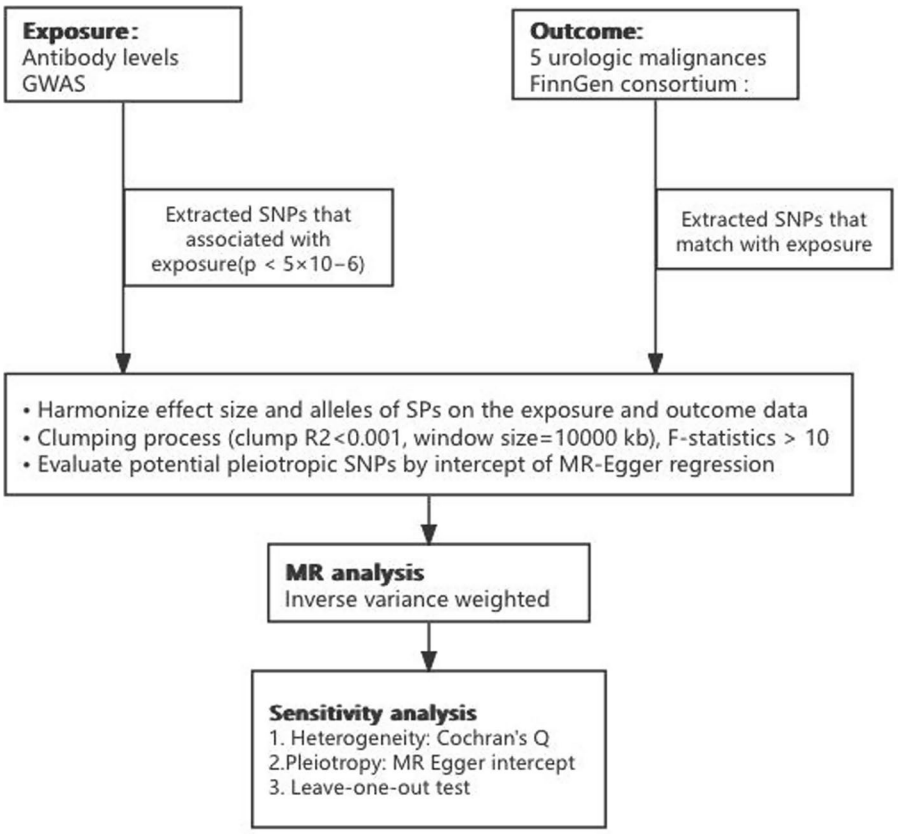

Fig. 1 the flow chat of MR analysis in the study

2.3 Selection of IVs

To ensure the stability and reliability of the MR analysis results, we screened the IVs using the following criteria:

1. SNPs significantly associated with the antibody levels ($p < 5 \times 10^{-6}$) were selected as IVs.
2. Independent SNPs were selected using a clumping procedure to avoid linkage disequilibrium (LD) ($r^2 < 0.001$ and distance > 10,000 kb).
3. SNPs with a minor allele frequency (MAF) below 0.01 were excluded.
4. Duplicate and palindromic SNPs were removed.
5. SNPs directly associated with the 5 urologic malignances ($p = 5 \times 10^{-8}$) were excluded based on data from Phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk/) [20].
6. To prevent the impact of weak IVs, we calculated the F-statistic (F) using the formula: $F = R^2 \times (N - 1 - K) / [(1 - R^2) \times K]$. R^2, indicating the fraction of exposure variance accounted for by the IVs [21], was estimated using an equation that incorporates the minor allele frequency (MAF) and the β value: $R^2 = 2 \times beta^2 \times MAF \times (1 - MAF)$. "N" represents the sample size, while "K" indicates the number of IVs. IVs with $F < 10$ were excluded, as $F > 10$ is generally considered the threshold for strong IVs [22].

2.4 Statistical analysis

All analyses were conducted using R 4.3.2 software (http://www.Rproject.org). The "Two-SampleMR", "ggplot2", "foreach" and "MRPRESSO" packages were utilized for statistical analysis.

A bidirectional MR analysis was performed to evaluate the reciprocal causal association between antibody levels and five urologic malignances using two samples. The IVW method was the main technique for estimating causality, aggregating the Wald ratios of individual SNPs to evaluate outcomes. β-values and standard errors were used to report continuous outcomes, while odds ratios (OR) within 95% confidence intervals were used for binary outcomes.

Statistical significance was determined by IVW P-values below 0.05 and consistent directions of IVW and MR-Egger. Statistical significance was also determined using Bonferroni-corrected two-sided P-values with thresholds set at 0.000543 (0.05/92) for antibody levels. P-values below 0.05 but above the Bonferroni-adjusted thresholds were considered to suggest a possible connection. If a p-value below 0.05 using the IVW method, consistent estimates from MR-Egger, weighted median, and IVW methods, the significance of causality can be determined.

2.5 Sensitivity analysis

The MR-Egger method was employed to detect horizontal pleiotropy, with an intercept p-value < 0.05 indicating the presence of pleiotropy. The MR-PRESSO technique was used to detect possible anomalies and reassess causality following their exclusion. Cochran's Q value assessed the level of diversity. The results of the MR-Egger intercept test and the MR-PRESSO global test were both non-significant ($p > 0.05$), indicating the absence of horizontal pleiotropy. Each SNP's impact on the overall causal estimate was confirmed using leave-one-out analysis.

3 Result

3.1 Clear cell renal cell carcinoma

Seven antibodies were identified as significantly associated with the risk of ccRCC (Supplementary Table 1). Five antibodies were found to be negatively associated with the risk of ccRCC, including Varicella zoster virus glycoproteins E and I (OR = 0.79, $p = 0.0035$) and Herpes simplex virus 1 mgG-1 (OR = 0.79, $p = 0.015$), while two show a positive correlation, such as Epstein-Barr virus(EBV) VCA p18 (OR = 1.41, $p = 3.06 \times 10–7$).

3.2 Renal pelvis cancer

EBV EBNA-1 and VCA p18 are associated with a reduced risk of renal pelvis cancer, with odds ratios of 0.72 and 0.66, respectively (Supplementary Table 1).

3.3 Bladder cancer

The study identified some significant associations between specific antibodies and bladder cancer (Supplementary Table 1). Specifically, Human herpesvirus 6 IE1B and Human herpesvirus 7 U14 exhibited divergent impacts on bladder cancer risk, with odds ratios of 0.81 ($p = 0.0096$) and 1.27 ($p = 0.005$), respectively.

3.4 Prostate cancer

In our research, we have identified ten antibodies which are causally associated with prostate cancer (Supplementary Table 1). Among these, five have shown a positive correlation: Anti-cytomegalovirus IgG seropositivity, Cytomegalovirus pp150 antibody levels, EBV EA-D antibody levels, EBV EBNA-1 antibody levels, and EBV VCA p18 antibody levels, and the odds ratios are 1.04, 1.06, 1.11, 1.06, and 1.05, respectively. Others are negatively associated with the risk of prostate cancer, such as Human herpes virus 6 IE1B antibody levels (OR = 0.93, $p = 0.0238$).

3.5 Testicular cancer

There are 10 antibodies causally associated with testicular cancer (Supplementary Table 1). We found that EBV-related antibodies may reduce the risk of testicular cancer. For example, EBV VCA p18 antibody levels have an odds ratio of 0.72 ($p = 0.000699$). In contrast, polyomavirus-related antibodies are positively associated with the risk of testicular cancer. For instance, polyomavirus 2 JC VP1 antibody levels have an odds ratio of 1.34 ($p = 0.011$).

3.6 Sensitivity analysis

Heterogeneity in the MR analysis results was evaluated utilizing Cochran's Q test in both IVW and MR-Egger methods. The MR-Egger intercept and MR-PRESSO global test were utilized to detect horizontal pleiotropy. These evaluations of heterogeneity and pleiotropy are essential for ensuring the validity and strength of our conclusions.

A lack of heterogeneity or evidence of potential horizontal pleiotropy in clear cell renal cell carcinoma (ccRCC) and renal pelvis cancer was indicated (Supplementary Table 2).Conversely, significant heterogeneity and pleiotropy were noted in bladder cancer for EBV EBNA-1 antibody levels and Anti-polyomavirus 2 IgG seropositivity. In prostate cancer, significant heterogeneity and pleiotropy were observed in EBV EA-D antibody levels. Furthermore, significant horizontal pleiotropy was observed in testicular cancer with regards to Anti-varicella zoster virus IgG seropositivity and Varicella zoster virus glycoproteins E and I antibody levels.

3.7 Reverse mendelian randomization analysis

In conducting a reverse Mendelian randomization analysis (Supplementary Table 3), there were several causal relationships between antibodies and urologic tumors, such as the association between Helicobacter pylori GroEL antibody levels and renal pelvis cancer (OR = 0.96, $p = 0.0201$) and ccRCC (OR = 0.98, $p = 0.0026$).

4 Discussion

The rising incidence of urologic cancers worldwide has become a significant public health concern, particularly due to the aging population and increased exposure to various risk factors. Despite advancements in early detection and treatment, the etiology of many urological tumors remains poorly understood [23, 24]. This study examined the potential causal relationship between antibody-mediated immune responses to infectious pathogens and the incidence of urologic tumors through the application of Mendelian randomization (MR) techniques. The findings elucidated the intricate association between chronic infections and the pathogenesis of urologic cancers. The results indicate that chronic infections may significantly contribute to the initiation of urologic cancers via immune response mechanisms. These findings furnish novel evidence supporting the carcinogenic role of chronic infections in urologic tumors. This is particularly significant given that the anatomical and physiological characteristics of the urinary system render it more susceptible to the deleterious effects of such infections.

4.1 Causal associations between antibody levels and urologic tumors

Our study found that higher antibody levels against Varicella zoster virus glycoproteins E and I were associated with a reduced risk of ccRCC (OR = 0.79, $p = 0.0035$) in ccRCC. In contrast, elevated antibody levels against EBV VCA p18 were linked to an increased risk of ccRCC (OR = 1.41, $p = 3.06 \times 10^{-7}$). These findings suggest that immune responses to different viral infections may influence ccRCC development through distinct mechanisms.

For renal pelvis cancer, the study showed that higher antibody levels of EBV nuclear antigen 1 (EBNA-1) and viral capsid antigen p18 (VCA p18) were associated with a reduced risk of renal pelvis cancer, with ORs of 0.72 and 0.66, respectively. This suggests that EBV might play a protective role under specific conditions, particularly in the case of renal pelvis cancer.

Regarding bladder cancer, the analysis revealed a significant association between EBV EBNA-1 antibody levels and bladder cancer risk, as indicated by a Q test p-value of less than 0.05. This result suggests the possibility of horizontal pleiotropy, meaning that these genetic instrumental variables could influence bladder cancer risk through mechanisms other than antibody-mediated immune responses.

The results of our study indicated that several antibody levels are associated with viral infections, especially anti-cytomegalovirus IgG, cytomegalovirus pp150, EBV EA-D, EBV EBNA-1, and EBV VCA p18 are positively correlated with an increased risk of prostate cancer.

In testicular cancer, the study identified significant associations between anti-Varicella zoster virus IgG seropositivity, Varicella zoster virus glycoproteins E and I antibody levels, and testicular cancer. Although the MR-Egger pleiotropy test showed a p-value of less than 0.05, indicating potential horizontal pleiotropy, the MR-PRESSO analysis did not reveal significant distortion ($p > 0.05$).

4.2 Mechanisms of viral infections in urologic cancer development

The above study results suggest a potential causal relationship between pathogen infections and urologic tumors. However, to gain a deeper understanding of this association, it is essential to explore how pathogens interact with the host's immune response through their pathogenic characteristics to influence cancer initiation and progression. The following section will further elaborate on these possible biological mechanisms, including EBV activating oncogenic signaling pathways and the role of chronic inflammation in tumor formation.

Studies have shown that EBV latent membrane protein LMP-1 inhibits apoptosis and promotes tumor cell survival by activating the NF-κB and PI3K/Akt signaling pathways [25, 26]. Furthermore, EBV can integrate its genome into host cells, affecting gene expression, disrupting genomic stability, and activating oncogenic signaling pathways, which contribute to tumor development [27]. EBV can induce ectopic expression of CD137 through its latent membrane protein LMP1. CD137 signaling activates the p38-MAPK pathway and induces the expression of pro-inflammatory cytokines such as IL-6 and IL-8. These cytokines are closely associated with tumor progression, metastasis, and poor patient prognosis. This indicates that EBV not only promotes tumor growth through immune evasion mechanisms but also directly contributes to the malignant phenotype of tumors via CD137 signaling [28]. These mechanisms may play a significant role in the pathogenesis of bladder cancer and ccRCC.

4.3 Role of chronic inflammation in tumor progression

Chronic inflammation is widely recognized as one of the key factors in cancer development [29]. The persistence of chronic inflammation leads to repeated physical and physiological damage to tissues, which can disrupt the structure and function of normal cells. This ongoing damage makes cells more susceptible to abnormal proliferation and malignant transformation [30]. During chronic inflammation, immune cells release large amounts of pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-1β. These cytokines not only amplify the inflammatory response [31, 32] but also promote tumor cell proliferation and survival by activating signaling pathways [33–35]. Additionally, pro-inflammatory cytokines can modulate the tumor microenvironment, supporting angiogenesis and metastasis, thereby facilitating tumor progression [36]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) produced during chronic inflammation are highly reactive free radicals that can directly damage intracellular DNA, proteins, and lipids [37]. Oxidative damage to DNA, coupled with incomplete repair, can lead to the accumulation of genetic mutations, thereby increasing the risk of cellular transformation and cancer development [38].

4.4 Host immune response and microbial pathogenicity

The damage response framework in the literature emphasizes that microbial pathogenicity is not solely dependent on the characteristics of the microorganism but is also closely related to the host's immune response [39]. An excessive immune response can lead to tissue damage [40], while a weak immune response may allow the microorganism to persist [41], resulting in chronic infection and potential carcinogenic effects [42]. In the development of urologic tumors, the intensity and type of host immune response may be critical factors in determining disease outcomes.

4.5 Potential of oncolytic virus therapy in urologic cancer

In recent years, research on oncolytic viruses has provided new perspectives on cancer treatment. Oncolytic viruses are a class of viruses that can selectively infect and kill tumor cells while also stimulating the host's antitumor immune response [43–46]. This mechanism makes oncolytic viruses an important direction in cancer immunotherapy. For example, studies have shown that oncolytic herpes simplex virus (HSV), like Talimogene laherparepvec (T-VEC), an oncolytic virus therapy based on the herpes simplex virus type 1 (HSV-1) [47], can infect tumor cells, inducing tumor cell lysis and death. The release of tumor antigens further activates the host's immune system, leading to sustained immune surveillance against other tumor cells [48–51]. In urologic tumors such as renal cell carcinoma, oncolytic virus therapy may become a promising strategy by directly killing tumor cells and activating the host's antitumor immune response, thereby inhibiting tumor growth.

4.6 Limitations of the study

Although this study used the MR approach to provide new insights into the potential causal relationship between antibody immune responses and urologic tumors, several limitations must be discussed.

1. Validity of IVs: The effectiveness of MR relies heavily on the selected IVs meeting the assumptions of strong relevance, independence, and exclusion restriction. In this study, although we carefully chose genetic variants associated with antibody levels as IVs, there may still be undetected pleiotropy, which could impact the accuracy of causal inference. Specifically, MR-Egger analysis indicated the presence of horizontal pleiotropy in some associations, suggesting that future research should focus on optimizing the selection of IVs and conducting more detailed sensitivity analyses.

2. Sample Representativeness: The antibody level data used in this study were derived from a limited population sample, which may not fully represent the general population. Additionally, the level of pathogen exposure and immune response can vary across different populations, potentially limiting the generalizability of the results. Future studies should aim to expand sample sizes and validate these findings in populations with diverse racial and geographic backgrounds.

3. Cross-Sectional Nature of the Data: This study's analysis was based on cross-sectional data, which precludes consideration of the temporal relationship between antibody levels and tumor development. After pathogen infection, antibody levels may fluctuate across different stages, and these stages may correlate with varying levels of cancer risk. Longitudinal studies in the future will be necessary to better understand the dynamic changes in antibody immune responses during tumorigenesis.

4. Focus on Antibody Levels: This study primarily focused on the relationship between antibody levels and urologic tumors, without considering other potential biomarkers, such as cellular immune responses or inflammatory markers. These factors may play a significant role in the development of urologic tumors, and future research should aim to incorporate a more comprehensive evaluation of immune responses.

5. ORs for the associations between viral antibodies and prostate cancer are all close to 1 (1.04, 1.06, 1.11, 1.06, and 1.05, respectively).This could imply a limited involvement of these viral antibodies in the development of prostate cancer, or it might indicate that the study did not fully control for confounding factors.

5 Conclusion and prospect

This study, through Mendelian randomization analysis, revealed a potential causal relationship between antibody immune responses to pathogen infections and urologic tumors. The results provide new insights into the role of chronic infections in urologic tumors, particularly highlighting the potential impact of Epstein-Barr virus (EBV) and varicella-zoster virus on bladder cancer, clear cell renal cell carcinoma, renal pelvis carcinoma, and testicular cancer. Although some associations showed weak effects, the findings suggest that pathogen infections may contribute to the development and progression of urologic tumors by modulating host immune responses, chronic inflammation, and genomic instability.

Future research should further investigate the specific biological mechanisms of these viral infections, particularly their complex interactions with host immune responses. Additionally, based on the findings of this study, prevention and treatment strategies targeting relevant pathogens, such as vaccination and antiviral therapy, could offer new approaches for the prevention and management of urologic tumors. The potential of oncolytic viruses, combined with immunotherapy, as an emerging treatment modality in urologic tumors also warrants further exploration.

In summary, this study underscores the importance of considering pathogen infections and their associated immune responses in the etiology of urologic tumors, and it points the way forward for future research and clinical applications.

Author contributions The study was designed by C.W., Q.Z., Q.L., and Y. W. downloaded and analyzed the data. C.W. drafted the manuscript, which was reviewed by X.C. The final version of the manuscript has been reviewed and approved for submission by all the authors. All the authors have read and agreed to the published version of the manuscript.

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Data availability The data is available within the manuscript or in the supplementary information files.GWAS summary statistics will be available through the NHGRI-EBI GWAS catalog. Data related to urologic malignances GWAS can be acquired from the FinnGen Consortium version R10.

Declarations

Ethics approval and consent to participate Local laws and institutional policies did not require written informed consent for this study. According to national laws and institutional policies, the study did not require ethical approval or consent.

Competing interests The authors declare no competing interests.

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