The Influence of Oral Microbiome on Oral Cancer Etiology

Oral Mikrobiyomun Oral Kanser Etiyolojisindeki Etkisi

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ABSTRACT

Research on the etiology of cancer suggests that bacteria playing a role in inflammatory processes, in addition to factors such as genetic factors, tobacco and alcohol use, environmental factors, aging, nutrition, and family history, can contribute to the development of cancer in the oral cavity and body. Research evaluating the relationship between inflammation and cancer demonstrates that cancer is not only a cellular-level process but also a complex one involving interactions with the organism's immune system. Studies investigating the relationship between oral cancer and the microbiome emphasize the significant impact of identifying the disease's pathogenic mechanisms on early diagnosis and determining effective treatment strategies. It has been shown that periodontal disease, in particular, may be influential in the development of oral cancer, various bacteria may play a role in cancer development, and changes in the oral microbiome may affect cancer prognosis. Research on the potential roles of bacteria such as C. albicans, Porphyromonas gingivalis, Fusobacterium nucleatum, Treponema denticola, and Streptococcus spp. in the development of oral cancer may facilitate the development of new approaches in cancer treatment. In this context, further research into the effects of the oral microbiome on cancer development and prognosis is crucial.

Keywords: *Oral cancer, microorganism, etiology, periodontal disease*

ÖZ

Kanser etiyolojisi üzerine yapılan araştırmalar, genetik faktörler, tütün ve alkol kullanımı, çevresel faktörler, yaşlanma, beslenme, aile öyküsü gibi faktörlerin dışında enflamatuvar süreçlerde rol oynayan bakterilerin de oral kavitede ve vücutta kanser gelişimine katkıda bulunabileceğini ortaya koymaktadır. Enflamasyon ve kanser ilişkisinin değerlendirildiği araştırmalar, kanserin sadece hücresel düzeyde değil, aynı zamanda organizmanın bağışıklık sistemiyle olan etkileşimlerini de içeren kompleks bir süreç olduğunu göstermektedir. Oral kanser ile mikrobiyom arasındaki ilişkiye yönelik araştırmalarda hastalığın patojenik mekanizmalarının belirlenmesinin erken teşhiste ve etkili tedavi stratejilerini belirlemede önemli bir etkiye sahip olduğunu vurgulamaktadır. Özellikle periodontal hastalığın oral kanser gelişiminde etkili olabileceği, çeşitli bakterilerin kanser gelişiminde rol oynayabileceği ve oral mikrobiyomdaki değişikliklerin kanser prognozunu etkileyebileceği gösterilmiştir. C. albicans, Porphyromonas gingivalis, Fusobacterium nucleatum, Treponema denticola ve Streptococcus spp. gibi bakterilerin oral kanser gelişimindeki potansiyel rolleri üzerine yapılan araştırmalar, kanserle mücadelede yeni yaklaşımların geliştirilmesine olanak sağlayabilir. Bu bağlamda, oral mikrobiyomun kanser gelişimi ve prognozu üzerindeki etkilerinin daha detaylı şekilde araştırılması önem arz etmektedir.

Anahtar Kelimeler: *Oral kanser, mikroorganizma, etiyoloji, periodontal hastalık*

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INTRODUCTION

Cancer is defined as the disruption of mechanisms that regulate cell proliferation, leading to the uncontrolled growth of atypical cells that replace healthy tissues and ultimately render the organism dysfunctional. In healthy cells, growth is tightly regulated by mechanisms that initiate and halt proliferation, and upon completing their normal lifespan, cells are eliminated via a process known as "apoptosis," or programmed cell death. (Figure 1) Apoptosis is a crucial mechanism that plays a critical role in cell renewal, immune system development, embryonic growth, and chemical-induced cell death, as well as in maintaining homeostasis in adult tissues.[1-3] Disruptions in this mechanism have been shown to contribute to various developmental, inflammatory, degenerative, and neoplastic diseases. Research on cancer development in relation to apoptosis underscores the complexity of cellular control mechanisms.[1,4,5] Specifically, factors such as chronic inflammation, increased cellular stress, and the accumulation of DNA damage can disrupt normal cellular balance, creating conditions that favor the proliferation of atypical cells. Thus, the multifactorial nature of cancer emerges from the convergence of various contributing factors. Additionally, investigations into the relationship between inflammation and cancer indicate that cancer is not merely a cellular phenomenon but also involves complex interactions with the immune system of the organism.

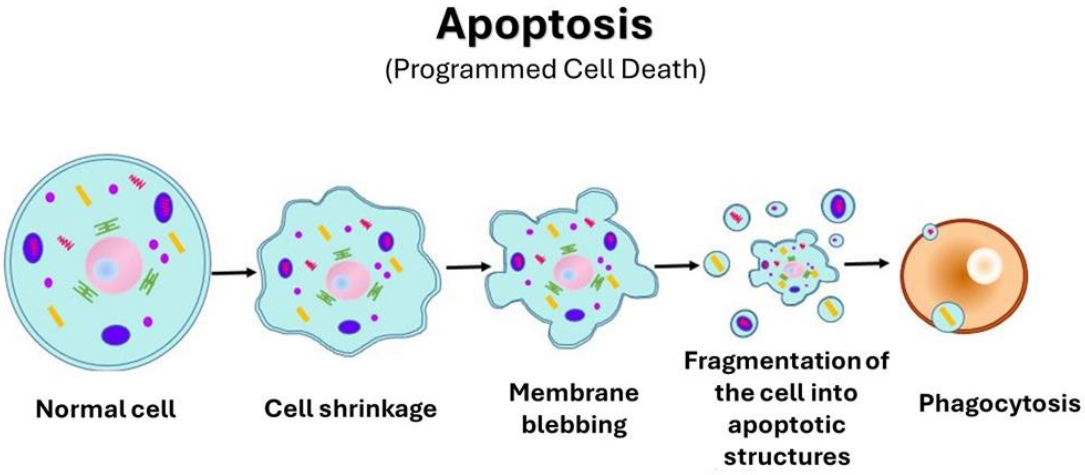

Figure 1: After completing its normal lifespan, the cell undergoes apoptosis and is then phagocytosed.[5]

Oral Microbiome and Cancer

Research on cancer etiology suggests that, in addition to well-known causes, approximately 15-20% of all cancers are associated with chronic inflammation.[6] Literature reports indicate that chronic inflammation induces both local and systemic immunosuppression.[7] In the development of oral cancer, carcinogenic alterations and inflammatory triggers act through an interrelated intrinsic and extrinsic pathway contributing to carcinogenesis. (Figure 2)

Intrinsic factors include genetic and epigenetic events, which, through oncogene activation or tumor suppressor inactivation, induce malignant transformation in keratinocytes and promote the production of inflammatory cell mediators associated with cancer. Active cytokines and chemokines produced during chronic inflammation, along with prostaglandins, reactive oxygen species, and various transcription factors, directly or indirectly affect eukaryotic cell cycles and signaling pathways, inhibiting apoptosis and promoting cell proliferation. Extracellular pathway is associated with an underlying inflammatory /infectious condition, activating transcription factors responsible for tumor development through produced inflammatory cytokines, thus supporting carcinogenesis. Both mechanisms lead to the production of transcription factors that sustain inflammation and cancer, ultimately fostering a microenvironment in which inflammation and cancer mutually reinforce each other.[8-10] Consequently, chronic inflammatory disorders such as oral lichen planus, oral submucous fibrosis, and oral discoid lupus erythematosus are recognized as conditions predisposing to the development of oral squamous cell carcinoma (OSCC), which is the most common malignancy of the oral cavity.[9]

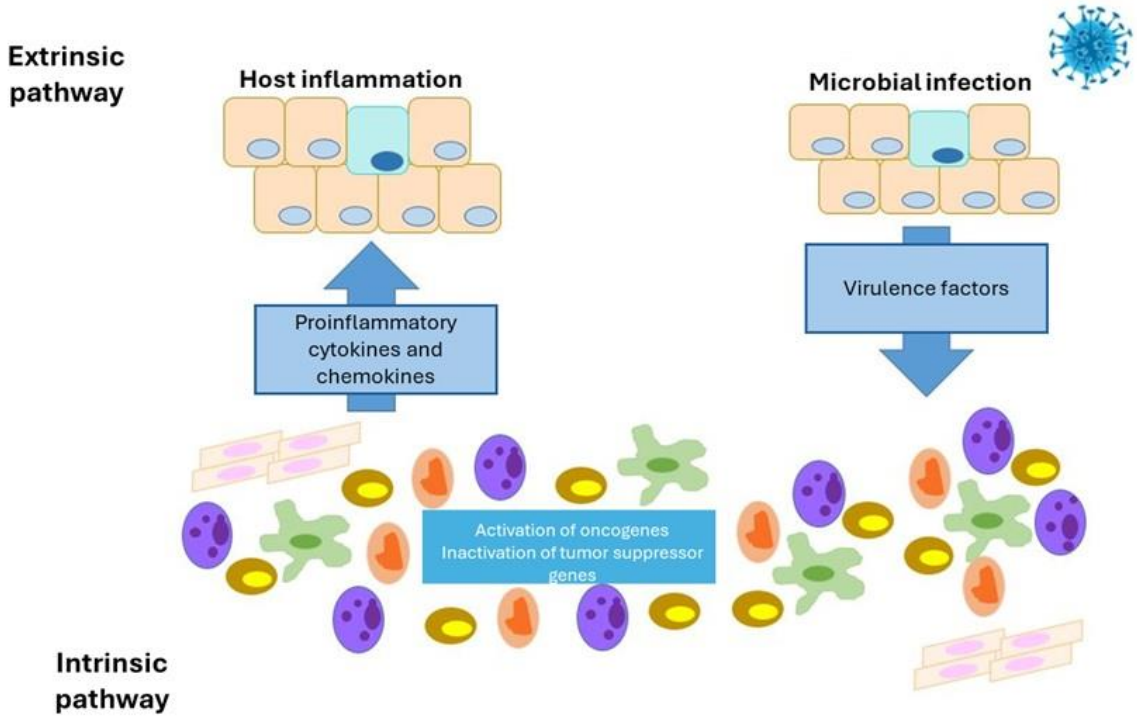

Figure 2: Both the intrinsic pathway, composed of genetic and epigenetic factors, and the extrinsic pathway, which triggers the production of inflammatory cytokines, play a role in initiating carcinogenic changes in the oral mucosa. As a result of both pathways producing inflammatory mediators and transcription factors that induce cancer formation, a microenvironment is created where inflammation and cancer feed and promote each other.[8]

The primary etiological factors contributing to cancer development are genetic predisposition, tobacco and alcohol consumption, environmental factors, aging, diet, lifestyle, stress, family history, and infections.[7] In addition to the mediators produced during local inflammatory processes in the oral cavity, bacterial components that induce inflammation are also thought to contribute to cancer development at the systemic level.[6,7,11-14] (Figure 2) The International Agency for Research on Cancer (IARC) currently classifies 11 microorganisms as "carcinogenic" to humans. These microorganisms include *Helicobacter pylori*, Hepatitis B and C viruses, *Opisthorchis viverrini*, *Clonorchis sinensis*, Human papillomavirus, Epstein-Barr virus, Human herpesvirus 8 (HHV-8), Human T-cell Lymphotropic Virus 1 (HTLV-1), *Schistosoma haematobium*, and Human Immunodeficiency Virus-1 (HIV-1).[7,15] *Helicobacter pylori*, which has the most well-established association with cancer development in humans, is classified as a class I carcinogen.[10,15,16] Since *Helicobacter pyl*ori was recognized as an agent causing gastric cancer,[17-19] significant evidence has emerged suggesting that oral bacteria also play a role in cancer development within the body.[7,13] It has been demonstrated that microorganisms not only initiate chronic inflammation but also contribute to cancer development by triggering the production of carcinogens such as N-nitroso compounds and acetaldehyde.[10,15,20,21] Acetaldehyde, a highly potent genotoxic metabolite, is a metabolic byproduct of ethanol and is produced through the oxidation of ethanol by the oral microbiota.[15,22] It has been determined that the produced acetaldehyde causes DNA damage in oral epithelial cells.[23] The increased production of acetaldehyde in the oral microbiota of chronic smokers suggests that, alongside key risk factors such as alcohol and tobacco use, the oral microbiome should also be considered a synergistic risk factor or cofactor.[15,21]

Research on the relationship between oral cancer and the microbiome emphasizes that identifying the pathogenic mechanisms of the disease has a significant impact on early diagnosis and the development of effective treatment strategies.[18] Given that structural changes in the oral microbial ecosystem support chronic inflammatory processes in the oral cavity and facilitate tumor progression,[18,24] poor oral hygiene and periodontal disease have been reported to alter bacterial ecology and may be associated with oral cancer independently of other risk factors.[16,25-28]

Periodontitis is defined as a chronic inflammatory disease caused by specific bacteria, and the bacteria responsible for this condition can persist by resisting immune responses, particularly when the disease remains untreated.[29,30] Inflammation caused by periodontitis not only leads to severe damage both locally and systemically,

but also contributes to malignant tissue transformation by enhancing the synthesis of carcinogenic compounds, by inhibiting cellular apoptosis, or both.[25,28,31-33] Various studies have demonstrated that periodontal pathogens, primarily *Porphyromonas gingivalis, Fusobacterium nucleatum*, and *Treponema denticola*, as well as other pathogens such as *Streptococcus sp., Peptostreptococcus sp., Prevotella sp., Capnocytophaga gingivalis, Veillonella, Actinomyces, Clostridium, Haemophilus*, and members of the *Enterobacteriaceae* family, are positively associated with lesions carrying a risk of oral cancer (oral potentially malignant disorders—OPMD) and oral cancers.[17-19,28,29,32,34-38]

Porphyromonas gingivalis, Porphyromonas catoniae, and *Fusobacterium nucleatum* have the capacity to enhance immune receptors and disrupt tight junctions between cells. Therefore, they are believed to be responsible for the oral epithelial changes occurring during the carcinogenesis process.[15,39] It has been found that *Fusobacterium, Peptostreptococcus, Neisseria*, and *Parvimonas* populations have increased in samples taken from OSCC cases compared to healthy controls, and these microorganisms have been more prevalent in advanced-stage cancer cases than in early-stage disease.[16] A study in which microbiome samples were collected and analyzed using the oral rinse method after surgery has demonstrated that the re-emergence of commensal bacteria such as *Streptococcus* and *Rothia*, along with the reduction of periodontopathogens such as *Capnocytophaga, Prevotella 7*, and *Leptotrichia*, contributed to increased survival rates six months after surgery.[40]

The literature includes numerous studies on different microbial families that may be associated with the development and prognosis of OSCC lesions. The most frequently highlighted pathogenic microorganisms and their mechanisms of action are presented below.

Porphyromonas gingivalis

P. gingivalis is an anaerobic gram-negative bacterium which is one of the most significant pathogens implicated in the development of chronic periodontitis. In addition to periodontitis, *P. gingivalis* has been associated with various oral and systemic diseases, including Alzheimer's disease, gastrointestinal cancers, and oral cancer.[17] Numerous studies have elucidated the mechanisms through which it promotes cancer development.[3,14] It has been reported that *P. gingivalis* inhibits programmed cell death in primary gingival epithelial cells, accelerates gingival epithelial cell proliferation, promotes the metastatic spread and invasion of OSCC cells, and induces chronic inflammation—a potential pathway contributing to carcinogenesis.[41] In a study conducted by Liu et al. (2020), *P. gingivalis* was found to inhibit the phagocytosis of OSCC cells by macrophages, enhance the expression of genes encoding pro-tumor molecules in OSCC cells, and accelerate the formation of an immunosuppressive tumor microenvironment. As a result of these effects, a novel mechanism through which *P. gingivalis* promotes OSCC progression has been revealed.[41] The ability of bacteria to enhance the "irregular and unlimited proliferation capacity"—which is a hallmark of tumor cells—is considered a pro-tumorigenic effect that supports tumor formation. This characteristic is prominently exhibited in the cells of tissues infected by *P. gingivalis*.[3,19] It has been demonstrated that *P. gingivalis* positivity is higher in patients with TNM (tumor, lymph node, and metastasis) stage III-IV disease, poor differentiation, and lymph node metastasis.[3] Studies have indicated that apoptosis is inhibited in infected epithelial cells, resulting in the development of an anti-apoptotic phenotype associated with cancer.[42] Proteomic studies demonstrate that infection of gingival epithelial cells with *P. gingivalis* leads to alterations in specific protein concentrations and phosphorylation levels. These bacteria primarily affect pathways associated with cyclins, cyclin-dependent kinases, and the p53 protein, consequently, disrupting the regulation of the cell cycle.[42,43] Therefore, infection caused by *P. gingivalis* is considered a potential risk factor for oral cancer.

Fusobacterium nucleatum

F. nucleatum is a gram-negative, obligate anaerobic bacterium found in the oral cavity, urinary tract, intestines, and upper digestive tract of both healthy and diseased individuals.[44] However, the frequent detection of *F. nucleatum* in various oral and systemic infections including periodontitis, angina, lung abscess, chronic otitis, sinusitis, peritonsillar, cerebral, and gynecological abscesses, inflammatory bowel disease, ulcerative colitis, Crohn’s disease, neonatal sepsis, Lemierre’s syndrome, and infective endocarditis, has led to its identification as a potent opportunistic pathogen.[44] As one of the most common species causing periodontitis and extraoral infections, *Fusobacterium nucleatum* has been detected at higher levels in the tissue and saliva samples of head and neck squamous cell carcinoma patients compared to healthy controls. Consequently, it has been suggested that this bacterium may play a role in the development of gastrointestinal and oral cancers.[15,17,28,38] Its presumed carcinogenic potential has been attributed to its pro-inflammatory effect, which occurs primarily through the induction of various cytokines, including TNF-α, IL-6, IL-8, IL-10, and IL-12.[44,45] Additionally, *Fusobacterium nucleatum* facilitates the formation of biofilms by enabling the aggregation of various species, acting as a crucial "bridge" between early and late colonizers. The frequent co-detection of *F. nucleatum* and *P. gingivalis* in oral biofilms suggests that *F. nucleatum* colonizes the environment before *P. Gingivalis*, and is essential for its establishment. Consequently, *F. nucleatum* and

P. gingivalis may collaborate to initiate neoplastic changes by triggering chronic inflammation.[46] Both *P. gingivalis* and *F. nucleatum* facilitate cancer cell invasion and metastasis by inducing the production of matrix metalloproteinases (MMP-2, MMP-13, and MMP-9), which play a role in pathological processes associated with extracellular matrix (ECM) degradation, including tumor invasion and metastasis.[46,47] Moreover, in addition to cytokines, reactive oxygen species generated by *F. nucleatum* infection contribute to cancer development by inducing mutations, genomic instability, and epigenetic changes. These cytokines can activate key transcription factors such as NF-κB and STAT3 in oral premalignant cells, subsequently promoting malignant processes such as proliferation, invasion, and metastasis.[46] Another potential mechanism explaining the contribution of *F. nucleatum* to oral carcinogenesis suggests that its infection promotes cell survival and migration.[17] In treatment-resistant patients, the oral microbiome plays a role in the prognosis of OSCC cases, and the low survival rate, aggressive nature of the tumor, and increased risk of metastasis may be associated with *F. nucleatum*.[21,39]

Treponema denticola

T. Denticola is a gram-negative anaerobic spirochete that constitutes a small fraction of the normal oral microbiota. It has been shown to possess various characteristics including motility, proteolytic activity, adhesion to epithelial cells, cytotoxicity, induction of bone resorption, and modulation of immune responses.[17] Being one of the most frequently associated spirochetes with periodontitis, *T. denticola* has also been implicated in the development of OSCC and oropharyngeal squamous cell carcinoma.[28,38,48] The association between *T. denticola* and OSCC is largely attributed to the effects of cytokines such as MMP-8 and MMP-9, which are linked to chronic inflammation, as well as its immunomodulatory capacity associated with various virulence factors including surface protein complexes, periplasmic flagella, and CTLP (chymotrypsin-like protease).[17,38] *T. denticola* has been reported to regulate the cell cycle in OSCC cells by activating the TGF-β signaling pathway and increasing the mRNA expression of TGF-β1, -β2, and -β3.[28] Additionally, it has been shown to enhance cell proliferation, particularly through a TGF-β1/Smad-dependent mechanism.[28]

Streptococcus spp.

Streptococcus anginosus is considered a significant factor in the development of head, neck, and esophageal cancers.[17,38,49,50] The frequent detection of *S. anginosus* in the cervical lymph nodes of OSCC patients suggests that damaged oral mucosa facilitates the colonization of *S. anginosus*, thereby accelerating bacterial drainage to the cervical lymph nodes.[17] The potential mechanism by which *S. anginosus* contributes to cancer development is based on its ability to enhance NO and COX-2 production, leading to DNA damage in infected tissues, which subsequently promotes carcinogenesis.[17] In addition to *S. anginosus*, other streptococcal species associated with OSCC include *Streptococcus constellatus, Streptococcus salivarius, Streptococcus gordonii*, and *Streptococcus parasanguinis*.[38]

Oral Micobiome and Oral Cancer

The fungal communities of the oral ecosystem are referred as the "oral micobiome." The species of *Candida*, which are found in approximately 80% of the population, are closely associated with OPMD and OSCC.[13,14,28,51,52] It is known that *Candida* is a member of the oral flora in healthy individuals, but can become pathogenic under certain conditions, particularly in immunocompromised patients leading to various opportunistic acute and chronic infections.[28,53] Oral candidiasis, caused by the overgrowth of *Candida* species (especially *C. albicans*), is the most common fungal infection of the oral mucosa.[53] Candidal infections contribute to the development of oral cancer by inducing pro-inflammatory cytokines and promoting the production of carcinogenic substances such as nitrosamines and acetaldehyde.[36,53] The increase in the number and density of Candida colonies can damage host cells, thereby promoting cancer development and potentially contributing to the progression of OPMDs into OSCC.[51,53] A systematic review on the relationship between candidal infections and oral leukoplakia, which has the highest incidence among OPMDs and carries a risk of malignancy, has shown that *Candida* may play a role in malignant transformation.[54] It has been found that the risk of developing oral cancer is three times higher in patients with *Candida* infection,[38] and the likelihood of *Candida* presence in the oral cavity of oral cancer patients is significantly higher compared to those without oral cancer.[28] Therefore, *C. albicans* has been considered an independent risk factor in the development of oral carcinoma.[54] The fact that chronic hyperplastic candidiasis exhibits a malignancy transformation rate ranging from 4.1% to 19.8%[52] also supports the relationship between *C. albicans* infection and the development of oral cancer.

Studies investigating the oral microbiome and cancer development report a wide range of microorganism loads with varying proportions. These significant differences are generally attributed to the lack of standardization in patient populations and microbiome research methods, as well as the heterogeneity in the studies. Older studies often focused on specific species and employed traditional methods such as bacterial culture, DNA-DNA hybridization, PCR, immunohistochemical staining, and denaturing gradient gel electrophoresis.[25] However, it has been reported that next-generation sequencing (NGS) shows higher sensitivity compared to these traditional methods. NGS technology has broad applications in understanding the ecology of microbial ecosystems and

determining the role of bacteria in health and disease,[31,55] and it offers significant advantages such as high efficiency and the absence of the need for targeting specific taxa.[55] Since NGS technologies have shorter read lengths, it is necessary to carefully select appropriate 16S rRNA regions for the detection of a broad and diverse range of bacteria.[56] Among the nine hyper-variable regions, the V3-V4 regions have the most significant impact on the identification of bacterial communities.[21,56,57] Next-generation DNA sequencing systems allow for highly accurate and ultra-fast sequencing. The microbial genome sequences obtained through this method provide researchers with exceptionally rich and unique information that cannot be obtained by any other experimental technique.[55,58] This method helps in the comprehensive understanding of the functional dynamics of microbial communities, and thus, it can offer a new perspective on microbial pathogenesis, provide detailed characterization of microorganisms involved in the cancer development process, and be used to identify appropriate bacterial taxa for diagnosis or risk assessment.[57]

CONCLUSION

In conclusion, although certain species within the oral flora are associated with oral cancer, studies have shown that changes in the oral microbiome occur before carcinogenesis.[57] The findings suggest that the oral microbiome plays a significant role in the complex pathogenesis of oral cancer; however, various contributing factors combine to influence the disease process. Therefore, due to the complexity of the conditions related to the microbiome, no single pathogen can be held responsible for the formation of carcinogenesis.[37] A deeper understanding of the oral microbiome is expected to not only aid in the development of future research and clinical applications, but also facilitate the identification of new strategies for the diagnosis, treatment, and prevention of oral cancer. Additionally, it may pave the way for the creation of personalized treatment approaches, such as the use of probiotics and prebiotics.

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