QUESTION B24: Are biofilms carcinogenic or associated with bone tumors?

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Response/Recommendation: Yes. Evidence suggests a potential role of biofilms in carcinogenesis, including bone tumors, which may occur through alteration of microbiome.

Level of Evidence: Moderate.

Delegate Vote:

Rationale

A comprehensive search strategy in PubMed and Medline Embase from inception till Nov 2024 using the appropriate MESH terms, developed by the librarians, was conducted. Search Results yielded 570 publications in English language. Two of the coauthors went through title and abstract and scored inclusion or exclusion, discrepant results were adjudicated by a third person. Thirteen full articles were included and reviewed in detail. One author prepared the draf manuscript and shared with other authors for comments and edits. The findings of the systematic review are presented here.

There is a growing evidence that bacterial biofilms play an important role in the development of various human diseases, including cancer. In order to facilitate their survival, biofilms induce immunological reactions and metabolic changes in the host, which can facilitate oncogene expression and cancer progression[1].

Biofilms can promote cancer by different mechanisms[1]. Biofilms can trigger inflammation that usually does not succeed in eliminating the biofilm-associated pathogens; persistent inflammation can cause DNA damage and promote the growth of cancer cells[2]. Biofilms can impact the efficacy of the host immune response[3], creating an environment prone to cancer development[4]. Some bacteria in biofilms can produce toxins acting as carcinogens[5]. Bacteria in biofilms can interfere on the host tissue metabolism[1]. Bacteria within the tumor microenvironment, referred to as the tumor microbiome, are involved in cancer progression[1; 6; 7]. While some bacteria and their biofilms mainly act as cancer promoters, there is growing evidence that a healthy gut microbiome and its metabolites can have an anti-tumor effect. On the other hand, it has been hypothesized that a dysbiotic gut can be the source of the intra-tumoral microbiome at different sites[8]. The health gut microbiome could travel from the intestinal tract to other organs via the bloodstream and nourish different organs such as the breast, pancreas, lungs and kidneys, and other organs. Thus, a dysbiotic gut could deliver pathological microorganisms to the bloodstream, and therefore contribute to the carcinogenesis and constitute the tumor microbiome at a particular site[1; 9-11].

Colon and colorectal cancers (CRC) are the most investigated types of cancer in terms of

biofilm involvement and its related carcinogenesis[12-19]. Dejea et al describe that colorectal cancer biofilms are usually detected on both, tumors and paired normal tissues. In their study, the paired normal tissue revealed biological changes relevant to oncogenic transformation. In addition, biofilm-covered mucosa was identified in a subset (~10–20%) of healthy individuals undergoing routine screening colonoscopy exhibiting epithelial changes like loss of E-cadherin from the apical zonula adherens, enhanced mucosal IL-6, and increased crypt cell proliferation[12; 14; 20]. Li and colleagues added that CRC initiation is triggered by local mucosal colonization with specific pathogens (drivers), and that subsequent changes in the peritumoral environment allow colonization by opportunistic (passenger) microbes, further facilitating disease progression[13]. The carcinogenesis of biofilms in CRC was investigated by Tomkovich et al in murine models[20]. They suggested that human colon mucosal biofilms, whether from tumor hosts or healthy individuals undergoing screening colonoscopy, are carcinogenic in murine models of CRC. This biofilm-related carcinogenesis may be initiated through chronic toxin-cellular changes[16; 17]. Accumulating evidence from both animal and human studies points towards the dysbiotic gut microbiome as a key player in the pathogenesis of CRC. Further studies that aim to evaluate the combination of antimicrobial and anti-carcinogenic substances on chemoprevention of CRC are warranted[18].

Kadam and colleagues describe the changes on the oral microbiome in tobacco-associated oral cancer[21]. In the context of oral carcinogenesis, notable pathogens include *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Candida* species and *Helicobacter pylori*[22; 23]. The authors describe that the use of tobacco alters the structure of the oral microbiome, including that of potentially malignant lesions. They also found that altered oral microbiomes influence key microenvironmental changes such as chronic inflammation, secretion of carcinogenic toxins, cellular and tissue remodeling, and suppression of apoptosis. Given this, it is clear that the bacterial and fungal biofilms in potentially malignant states are likely not passive entities, and could play a critical role in shaping potential malignant and carcinogenic conditions[21]. Recent studies have shown that oral microbiota play an important role also in the esophageal cancer (EC) initiation and progression, suggesting that oral microbiota is a new risk factor for EC[24]. The results showed that the composition of the microbes inhabiting the oral cavity could be perturbed with continuous factors such as smoking, alcohol consumption, and inflammation.

Biofilms leading to gastrointestinal cancers have also been investigated, in particular in the gallbladder. Over the past few decades, substantial evidence has supported that gut microbiota plays a critical role in promoting the progression of gallbladder cancer (GBC)[25]. In a subset of individuals, *Salmonella Typhi* colonizes the gallbladder causing an asymptomatic chronic infection. Epidemiological studies performed in regions where *S. Typhi* is endemic, revealed that the majority of chronically infected carriers also harbor gallstones, which in turn, have been indicated as a primary predisposing factor for the onset of GBC. It is now well recognized, that *S. Typhi* produces a typhoid toxin with a carcinogenic potential, that induces DNA damage and cell cycle alterations in intoxicated cells[26].

Nadler and colleagues suggest that biofilm occurs in urothelial cancer tissue indicating an association between biofilm formation and bladder cancer. In urology, the development of squamous cell carcinoma of the bladder due to the parasitic infection with *Schistosoma Mansoni*

is widely accepted. *Escherichia coli* is also responsible for 80% of all urinary tract infections. Recent findings suggest an altered urinary microbiome in patients with bladder cancer compared to healthy subjects[27].

Additionally, the possible involvement of biofilms in the breast oncogenesis has recently created curiosity, and *Staphylococcus epidermidis* has been implicated[28]. This study demonstrated that *S. epidermidis* is capable of forming biofilms that can create a sustained inflammatory environment through their metabolites and can induce DNA breaks in breast cells, promoting cellular proliferation, angiogenesis, and genetic instability.

Nejman et al developed a comprehensive analysis of the tumor microbiome, studying 1,526 tumors and their adjacent normal tissues across seven cancer types, including breast, lung, ovary, pancreas, melanoma, bone, and brain tumors[11]. The authors found that some bacterial pathways that can degrade metabolites known to be enriched in different kind of tumors. For example, degradation of hydroxyprolines by bacteria was enriched in bone tumors. Bone collagen is a main source of hydroxyproline, and many bone pathologies, like bone tumors, have been shown to result in elevated hydroxyproline levels[11; 29]. Patients with severe bone lesion such as that arising from malignant bone tumor and primary parathyroid adenoma as well as those with congenital systemic bone disease excrete significantly increased amounts of hydroxyproline in the urine. Hydroxyproline excretion is elevated in destructive bone tumor, in primary hyperparathyroidism, and in congenital systemic bone disease. In this case, the urinary hydroxyproline reflects the rapid rate of bone collagen degradation[30]. Hydroxyproline, can also be a marker for bone destruction in case of infections like osteomyelitis[31].

In conclusion, it appears that altered microbiomes in different tissues can lead to the development of cancer. However, the number of studies implicating biofilm formation and bone tumors is limited. Thus, further investigations examining the oncogenic role of biofilm formed in patients with orthopedic infections are warranted.

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