Liver Flukes and the Microbiota in Cancer

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Tumor development is a multifactorial process, influenced by both genetic and environmental pressures. A small number of chronic infectious agents have been designated carcinogenic, including viruses (hepatitis B, C and HPV), bacteria (Helicobacter pylori) and parasites (De Martel et al., 2012). Further, general microbial dysbiosis can contribute to the development of some cancers (Garrett, 2015), including in the biliary system (Avilés-Jiménez et al., 2016). In the Southeast Asian countries Thailand, Laos, Vietnam, and Cambodia, the liver fluke Opisthorchis viverrini is endemic, and chronic infection with this trematode is a known risk factor for development of the bile duct cancer cholangiocarcinoma (CCA). Understanding how O. viverrini infection contributes to CCA development or progression could lead to new therapeutic interventions for this notoriously hard to treat disease.

Multiple O. viverrini infection-induced pathways have been associated with tumorigenesis, including parasite secretion of a growth factor that facilitates wound healing, angiogenesis and cellular proliferation that contributes to transformation of bile duct cholangiocytes (Smout et al., 2015, 2009) and infection-induced chronic inflammation (Sripa et al., 2012). This is reminiscent of a growing number of inflammation-driven cancers that involve bacterial dysbiosis (Garrett, 2015). However, the local tissue microbiome has been an understudied component of CCA. Recent studies using a small animal model of O. viverrini-induced CCA demonstrated that fluke infection of Syrian golden hamsters altered commensal bacterial communities in the gastrointestinal tract and allowed translocation of several microbes into bile fluid (Plieskatt et al., 2013), indicating that microbial shifts associated with O. viverrini infection may influence CCA.

In this issue of EBioMedicine, Chng et al. (Chng et al., 2016) interrogate the microbiome of bile ducts isolated from O. viverrini-naïve and -infected CCA patients and report a number of distinct features in the bacterial composition of local tissues. All bile duct samples from CCA patients, independent of O. viverrini infection, harbor similar microbial communities comprised of taxa typically found in the gut. Based on comparison of these tumor samples to hepatic and gastric tissues of non-CCA patients, the authors suggest the existence of a bile duct-specific microbial signature. These findings will require verification in a prospective trial with robust matching of donor tissues and higher sample numbers. Despite the gross similarities between O. viverrini-naïve and -infected CCA bile duct microbiomes, Chng et al. identify microbial alterations that stratify based on O. viverrini status. In O. viverrini-naïve tumor samples, the genus Stenotrophomonas (a pro-inflammatory γ-proteobacter) was enriched. Notably, fluke-infected samples have higher abundance and prevalence of Bifidobacteria, which has been previously shown to produce high levels of bile salt hydrolase (BSH) and contribute to elevated levels of carcinogenic bile salt metabolic products (Sagar et al., 2015). However, in contrast to what has been seen in colon cancer, CCA tumors and adjacent non-cancerous hepatic tissue harbor very similar microbes, indicating that CCA-associated microbiome changes are systemic rather than tumor-specific. Together, the fluke-induced microbial changes reported by Chng et al. add to the growing body of literature demonstrating that helminths can alter the microbiota within mammalian hosts and show that the ability of helminths to modulate bacterial communities extends beyond the gut.

A final model is presented to suggest that the altered microbial composition of the O. viverrini-infected bile duct may promote tumor development. Specifically, the authors propose that O. viverrini infection and colonization of bile ducts with Bifidobacteria fosters a carcinogenic microenvironment through bacterial metabolic activity, suggesting that increased accumulation of bile acids and ammonia could enhance inflammation or genomic instability, similar to what has been reported in colitis-associated colorectal cancer (Louis et al., 2014). Together, the results implicate parasite and host interactions in the dysregulation of local physiology that contributes to carcinogenesis as O. viverrini alters the bile duct environment and promotes the proliferation of a new bacterial player (Bifidobacteria). Although the findings from these patient-based studies are intriguing, many questions regarding the relative contribution and mechanisms by which local microbiome shifts may influence the development or progression of CCA in the context of O. viverrini infection remain to be addressed.

We highlight the need for future studies to employ careful sampling design and to analyze microbial data with prudence. In the context of comparing CCA-associated bile ducts to healthy tissues and the potential mechanistic link that underlies O. viverrini infection, dysbiosis, and promotion of a carcinogenic microenvironment, the findings by Chng...
et al. must be interpreted with caution, as must all associational studies. In particular, the enrichment of specific microbes within human tumors should not be considered causative for tumorigenesis, progression or severity (Garrett, 2015). Nonetheless, the value of patient-based epidemiological studies is the provision of testable hypotheses for basic science experiments to determine the contribution, if any, of noted associations. The manuscript by Chng et al. should entice further investigation of how O. viverrini infection can affect microbial communities, the microbial metabolome, and the local immune microenvironment in CCA development and progression.

Conflicts of Interest
The authors declare no conflicts of interest.

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