See Article page 419.

Commentary: Lower airway microbiome and non–small cell lung cancer: The beginning of a bug story

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CENTRAL MESSAGE

Certain lower airway bacterial composition may be associated with increased risk of recurrence after resection of early-stage NSCLC.

Molecularly targeted therapy and immunotherapy have revolutionized the treatment for properly selected locally advanced unresectable stages IIIA/B and metastatic stage IV non–small cell lung cancer (NSCLC) for which durable responses and extended survivals have been observed.[1] Efforts have been made from many fronts to further improve the overall survivals of surgically treated early-stage NSCLC.[2] The 5-year survivals of high-risk stage IA (T1cN0) or stage IB (T2aN0), ranging from 68% to 77%, are not optimal.[3] Adjuvant therapy, either cytotoxic chemotherapy or molecularly targeted therapy (tyrosine kinase inhibitors for NSCLC with epidermal growth factor receptor–activating mutations), is not standard of care for stage 1 NSCLC. Not all patients with resected stage I NSCLC need adjuvant chemotherapy, and identification of those at risk for recurrence to give adjuvant therapy has been a topic of intense research in the last 2 decades. The paradigm is to define and validate prognostic markers identifying patients at risk for recurrence and predictive markers to guide the choice of the most effective adjuvant therapy. Identification of prognostic biomarkers has progressed from onco-protein expression in tumor cells using immunohistochemical staining of tumor tissues,[4] to molecular signatures using gene expression array of tumor cell lysates,[5] and most recently to identification of circulating tumor DNA in peripheral blood.[6] Prognostic biomarkers for NSCLC require vigorous clinical validation and are not ready for prime time.

An emerging field of cancer research focuses on the relationship between the microbial flora, normally symbiotic to the human host, and cancer. A simple search in PubMed (microbiome and cancer) shows an exponential increase in the number of publications in the last 2 years. Microbiome research, a large-scale study of the microbial flora, has shed light on the potential relationship between bacterial flora and cancers.[7] In this issue of the *Journal*, Patnaik and colleagues,[8] under the leadership of Dr Sai Yendamuri at Roswell Park, report their initial research results that describe the connection of the lower airway microbiome with the clinical outcomes of patients undergoing curative-intent lung resections. They define a microbiome signature that is associated with an overall lower survival (reminiscent of a prognostic biomarker) in a study set of 48 patients in whom saliva, bronchoalveolar fluid, and tumor tissues were prospectively collected in the perioperative period. This study is significant because it (1) is a collaborative effort of a team of clinicians, basic scientists, and biostatisticians equipped with powerful and sophisticated statistical software led by a thoracic surgical oncologist to conduct translational research on microbiome and lung cancer; (2) harnesses the vast power of bioinformatics to analyze the microbiome array atlas in search for a prognostic signature for early-stage lung cancer; (3) works on an "out-of-the-box" hypothesis and paradigm shift to define the connection between the distal airway microbiome and the tumor biology, and ultimately treatment outcome; and (4) merges the prognostic microbiome signature of poor outcome with tumor gene array data to offer a potential mechanism of the impact of specific airway microbiota on tumor oncologic aggressiveness and risk of recurrence.

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Compared with other molecular prognostic markers being developed and validated now, this seems like a ''baby step'' of a moonshot effort. We urge the readership not to be intimidated by the complex data being presented and the new ''language'' of microbiome research, and to look beyond that to appreciate the potential translational value of this ''cutting edge'' study. Thoracic surgeons learned the nuances of cancer molecular biology just a decade ago and have already incorporated that knowledge to translational research and clinical practice. Perhaps we should learn the new language of cancer microbiome and explore its potentials to push our field forward in decades to come.

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