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# Therapeutic Interception of Early Lung Adenocarcinoma Progression: Not Just How, but When?

In this issue of the *Journal*, Treekitkarnmongkol and colleagues (pp. 90–101) present data on a pathway of early adenocarcinogenesis of the lung, demonstrating the effect of lipocalin-2 on the development of KRAS-mutated lung adenocarcinoma (KM-LUAD) and suggesting that airways damaged by chronic obstructive pulmonary disease (COPD) show the effect of a high–lipocalin-2 microenvironment (1). Their experiments were based on an observed elevation of *Lcn2* in the nonneoplastic airways of mice with knockout of *Gprc5a* (2) followed by studies examining lipocalin-2 in these mice exposed to tobacco carcinogen, increased tumor development in $Lcn2^{-/-}$ mice, and translation into human tissues with COPD and LUAD.

The review of the literature of the relationship of LCN2 to human cancer would identify it as having a protumoral function (3–6), by mechanisms that include survival advantage through iron scavenging and enhancement of migration. In some tumor types, it is proposed as a target for therapy or, at a minimum, a biomarker for diagnosis or of aggressive behavior (7).

Although LUAD showed an increase in lipocalin-2, the authors show through their mouse model that loss of lipocalin-2 reduced antitumoral immune responses and enhanced a protumoral immune environment, such that the loss of *Lcn2* enhanced tumor formation. The induction of LCN2 was not seen in squamous carcinoma, occurring in KM-LUAD preferentially and by immunohistochemistry in tumor cells. An inverse relationship between NKX2-1 (TTF1) reactivity and LCN2 reactivity suggested differentiation away from club cell and type 2 pneumocyte, toward a gastric-type cell differentiation. In addition, the upregulation of *LCN2* was seen in COPD airways when compared with smokers without COPD but importantly included elevation in KM-LUAD from patients with COPD.

At first glance, there is a paradox—LCN2 is protumoral in several tumor types in prior reports yet here antitumoral. Also, LCN2 levels are high in LUAD, especially KM-LUAD. There are potential explanations for this type of paradox, which can include cell type or differentiation, differences in tumor microenvironment, and/or temporal switches in the stepwise progression toward neoplasia. Even among T1 adenocarcinomas, the antitumoral effect seems already lost; it is possible that the role of LCN2 in tumor initiation is different than a later role in cell migration. Additionally, it remains possible that non–tumor cell LCN2 becomes a factor in different phases of the disease. When we observe a tumor mass lesion, we are seeing the outcome of numerous potentially antagonistic tumor–host events that have occurred over time, which eventually fail to control tumor growth and spread. Such an explanation allows for an antitumoral effect for LCN2 that creates a balance between preneoplasia and cell death, a balance that accounts for a period of latency to adenocarcinoma development in COPD not seen for squamous or small cell carcinoma.

This could allow for risk stratification for the development of KM-LUAD that are smoking-associated LUAD among patients



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with COPD and an opportunity for therapeutic interception. It also begs the question of how we can prolong this antitumoral effect before it is superseded by other events.

Pathologists see a wide spectrum of tumor-associated stromal responses, from minimal in some invasive mucinous adenocarcinomas to some so exuberant as to almost obscure tumor cells. One element that is missing in the study of human tumors is the ability to associate these changes over time; imaging correlates provide some insight, but serial sampling of a primary lesion is very uncommon. It is possible that the mechanism proposed by these authors occurs at a time when the tumor is not clinically detectable or at a period of incipient neoplasia. Detection would require a signature that is recognizable in that incipient setting, rather than in the setting of a fully developed tumor mass (8, 9), and preferably by a relatively noninvasive approach. Observations in a mouse model allow for such temporal examination, and these insights are invaluable. But if we are to successfully intercept progression of lung adenocarcinoma, understanding these phases in human tumors becomes essential—identification of the proper at-risk population is one element, but catching the phase of tumor evolution that allows interception depends on the proper characterization of protumoral versus antitumoral milieu to achieve effective tumor suppression. The right targeted therapy given at the wrong time may not have the intended effect. Put a different way, it is a question not only of how we can prolong the antitumor effect of LCN2, but when it is too late to try.

It is also intriguing that this study may provide insight into the origin of histologic subtypes of adenocarcinoma. Could the epithelial-derived LCN2 antitumoral effect rely on the balance between a "molecular injured" club cell or pneumocyte and its native lung stromal microenvironment, and that this balance is disrupted when the epithelial cell acquires nonterminal respiratory unit differentiation ("gastric type") through loss of NKX2-1 (TTF1) expression (10, 11)?

The study shows the power of animal models to unearth myriad roles for the same molecule over stepwise tumor development, and that this temporal dimension is critical to understanding lung carcinogenesis, especially for adenocarcinoma in which the precursor lesions are either inaccessible in distal lung parenchyma or as yet unidentified (12). It also shows an imperfect human translation—will this mouse model be relevant to all LUAD, only KM-LUAD, all COPD-associated LUAD, or only KRAS-mutated, NKX2-1–negative LUAD? The existing complexity of tumor stromal interaction, which potentially can be dissected as a snapshot in a single human tumor (13), now has the added dimension of time, as demonstrated by the current study. Given the unknowns surrounding precursor lesions of adenocarcinoma, time of latency, and probability of progression, a more detailed road map of precursor lesions and preinvasive adenocarcinoma is a critical future direction toward successful therapeutic interception in early lung adenocarcinoma to exploit findings such as those demonstrated by this work. ■

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Alain C. Borczuk, M.D.
*Pathology and Laboratory Medicine*
*Weill Cornell Medicine*
*New York, New York*

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