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Raising the Flag for Mast Cells as a Novel Target in Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare, multiorgan disease, affecting primarily women during the childbearing years (1). Patients with LAM have proliferative, smooth-muscle–like cells within the lung and lymphatics, leading to both airway and lymphatic obstruction (2). An inherited form of LAM occurs in patients with tuberous sclerosis complex (TSC), with prevalence estimated at 26–49% of women with TSC and increased incidence with aging (3). Sporadic LAM occurs more rarely with an incidence estimated at 3.5 per 1 million females in the United States (4). From a pulmonary standpoint, women with this disease can present incidentally or, more often, with symptoms including dyspnea, cough, chylous effusions, or pneumothoraces (1).

Based on the high incidence of LAM in patients with TSC, studies historically focused on the role of the mammalian target of rapamycin (mTOR) signaling pathway. Loss of TSC gene function constitutively activates the mTOR signaling pathway, leading to cellular proliferation and survival in numerous disease states including LAM (5). mTOR activation is blocked by sirolimus, leading to a series of *in vitro* and preclinical *in vivo* studies in LAM that ultimately laid the framework for the landmark MILES (Multicenter International LAM Efficacy and Safety of Sirolimus) trial (6). This double-blind, placebo-controlled study of 89 women with LAM found that mTOR inhibition with sirolimus stabilized the decline in FEV_1 over a 1-year study (6). Although cessation of sirolimus in the 12-month follow up was associated with a resumed decline in lung function, the MILES trial was nevertheless transformative for the care of women with this rare disease, with efficacy and minimal side effects described out to 4 years of observational therapy (7, 8). However, it must be noted that inhibition of mTOR produces growth arrest, not apoptosis, in LAM cell cultures (9), rendering this treatment as transient and not fully curative (10–12). There is recurrence and/or growth of tumors noted upon cessation of therapy (6), and studies have proposed mechanisms by which TSC2-null cells develop resistance to mTOR inhibition over time (13). Therefore, despite the putative role of TSC2 in LAM, groups have wisely begun to investigate TSC2-independent pathways in disease pathogenesis (14–16) to increase the potential pipeline of therapies for this rare disease.

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In this issue of the *Journal,* Babaei-Jadidi and colleagues (pp. 431–444) have focused on the tumor microenvironment and identified a critical role for the mast cell in LAM nodule proliferation, adding an important and already targetable mTOR-independent pathway to the LAM armamentarium (17). The authors beautifully lay out a translational investigation by first identifying increased tryptase positive mast cell presence in LAM nodules, correlating with disease progression. They later evaluate how LAM cell–fibroblast coculture chemokines alter mast cell recruitment in a three-dimensional spheroid model system and show that tryptase release from the mast cell further augments fibroblast proliferation and the resultant size of the LAM spheroid. Tryptase inhibition reduces the LAM spheroid growth in an mTOR-independent manner, but combination with sirolimus had synergistic effects. The mast cell stabilizer cromoglycate reduced tryptase activity in an *in vivo* murine LAM model and alone significantly decreased the lung tumor burden similar to sirolimus therapy.

Although the data above is quite promising, particularly the LAM spheroid work, one area of concern is the lack of protease effect as a result of mast cell coculture. In fact, in LAM cocultures, mast cells have an inhibitory effect on protease activity as measured by gel zymography and cathepsin K activity. Parenchymal lung damage in LAM is widely accepted to be protease dependent (18–20), and the lack of effect of mast cell stabilizers on protease activity may foreshadow limitations of targeting the mast cell in LAM disease progression. In addition, although LAM spheroid work suggests a synergistic effect of mast cell stabilization and mTOR inhibition in LAM, the authors did not perform *in vivo* dual therapy studies, which would have strengthened the foundation for future clinical trials in patients with LAM.

This work by the Johnson laboratory is an incredibly important contribution to the LAM research community. Not discussed within the manuscript but worth mentioning is the fact that many women with LAM are initially diagnosed with asthma based on pulmonary function testing that includes the hallmark bronchodilator reversibility that may in part be mast cell related. Even after LAM diagnosis, almost half of patients use bronchodilators regularly (21). Some of the positive effects of β-adrenergic agonists in LAM (16) may be additionally attributable to direct mast cell stabilizing effects (22). In chronic obstructive pulmonary disease, mast cells lining the blood vessels, not the airway smooth muscles, were associated with airway hyperresponsiveness (23).

In summary, Babaei-Jadidi and colleagues have identified a novel mTOR-independent pathway to be targeted in LAM. Many tumors of patients with LAM do not exhibit *TSC* mutations (24–26) and express the tuberin protein (27, 28), underscoring the need for the LAM research community to identify mTOR-independent pathologic mechanisms that can account for the timing of onset and growth of tumors in patients with TSC, LAM, and sporadic LAM. Broadening the net to include other pathways can only aid the patient population; some patients have progression of disease despite mTOR inhibitor therapy, other patients have therapy-limiting side effects, and, most importantly, in a population of women in their childbearing years, patients may need to stop sirolimus in the setting of pregnancy. Understanding these constraints on sirolimus therapy for women with LAM, identification of efficacious and already available pharmacotherapies will aid in therapy, whether it be in early disease, in mTOR-intolerant patients, or in conjunction with sirolimus in patients with severe or rapidly progressive disease. Future studies would be expected to address potential synergy of cromoglycate and sirolimus in animal models and, ultimately, in the patient population. ■

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Electronic Health Records and Machine Learning for Early Detection of Lung Cancer and Other Conditions

Thinking about the Path Ahead

In this issue of the *Journal*, Gould and colleagues (pp. 445–453) describe an innovative use of machine learning with stored patient electronic health record (EHR) data to develop a risk model assessing the short-term risk of non-small-cell lung cancer (1). The study authors identified two primary applications of the approach in clinical practice, namely providing patients and providers with a tool to assist in personalized decision-making and identifying persons for outreach and for potential eligibility for lung cancer screening with low-dose computed tomography (LDCT).

The model developed by the study authors, denoted by "MES," used demographic information, smoking history, clinical data, and laboratory data that were available in EHRs in their health maintenance organization's (HMO's) data warehouse. The MES model showed better prediction of lung cancer diagnosis within 3–12 months than the current standard LDCT eligibility criteria (which are based only on age, pack-years, and years since quitting) as well as better prediction than a well-known risk model based on detailed smoking history and demographics (the PLCOm2012 model) (1, 2).

Uptake of LDCT screening following the initial B recommendation of the U.S. Preventive Services Task Force (USPSTF) in 2013 has been slow and limited, with currently (before coronavirus disease [COVID-19]) only an estimated 5–10% of eligible individuals undergoing LDCT screening (3). Therefore, there is a critical need to use strategies to substantially increase this rate. Although with shared decision-making not all eligible individuals will choose to be screened, a rate of 50% or higher is desirable and potentially attainable.

Around half of patients in this HMO had missing data on pack-years, meaning that final determination of USPSTF eligibility could not be made based on EHRs alone (1). Use of the MES model could help identify, among those with missing data, those patients more likely to meet the USPSTF criteria. In addition, by helping estimate risk, it could assist with shared decision-making and potentially encourage individuals to choose to be screened.

The USPSTF recently updated their lung cancer screening recommendation, increasing the eligible pool by lowering the age and minimum pack-year requirements (4, 5) Their recommendation states that there was insufficient evidence to "assess whether or not risk prediction model–based screening would improve outcomes" (5). An argument against using current risk models (e.g., PLCOm2012) is that they incorporate age as a risk factor and thus skew eligible individuals toward older individuals. Although older people are at a higher risk of lung cancer, they also represent fewer potential life-years saved by screening, so using risk-based criteria may increase the number of lives saved but not necessarily the years of life saved (5). In the MES model, age was one of the top 10 most informative features, suggesting that this same issue applies (1).

For HMOs, which do not rely on fee-for-service reimbursement from the U.S. Centers for Medicare and Medicaid Services or private insurers, there is some leeway in deciding whom to screen for lung cancer. Accordingly, they could use either standard risk models such as PLCOm2012 or models developed from EHRs—such as MES—to broaden their eligibility criteria for screening. However, most healthcare

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