

# New study lays groundwork for potential new anti-cancer therapy

June 8 2016

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Identifying the cell of origin is crucial to understanding how a tumor develops and metastasizes and for developing targeted therapies. Researchers have found evidence supporting a lymphatic endothelium origin for angiomyolipoma (AML) and lymphangiomyomatosis (LAM), two related tumors with previously unknown cellular origins. Furthermore, the newly identified lymphatic endothelial lineage shows translational potential for pharmaceutical treatment. Their findings are published in *The American Journal of Pathology*.

"As both AML and LAM are tightly linked processes, they are thought to be different manifestations of a common process," explained lead investigator Lucia Nieto Schuger, MD, of the Department of Pathology at The University of Chicago. "As a result of our investigation of the cell of origin for an AML cell line derived from a LAM patient, we were able to suggest a potential novel origin for LAM mechanistically dependent upon TSC [[tuberous sclerosis complex](#)] inactivation as well."

The researchers used an AML-derived cell line to determine whether restitution (re-expression) of the TSC2 protein would promote differentiation into the cell type from which AML arises. In this cell line and histological sections of AMLs, several embryonic lymphatic endothelial cell (LEC) markers consistent with LEC precursors were expressed. Upon TSC2 correction, AML cells matured immunophenotypically into adult LECs and showed functional attributes of this lineage. Such lymphatic mimicry observed in many cancers represents a curious enigma, but the molecular mechanisms for a 'failed'

or 'dysregulated' lymphatic system are striking, opening the door for development of improved therapies.

Previous clinical trials with rapamycin, the only FDA-approved drug for treating LAM and AML, have been only partially successful. Combined therapies with rapamycin followed by surgery, in the case of AML, or addition of second drug, particularly in the case of LAM, are therefore the focus of much attention.

The investigators found that the lymphangiogenesis inhibitor norcantharidin halted the proliferation of both TSC2<sup>+</sup> and TSC2<sup>-</sup> AML cells in vitro. Norcantharidin used in combination with rapamycin also produced promising preliminary results. "These studies showed an additive effect between rapamycin and norcantharidin, demonstrating preliminary effectiveness in repurposing an anti-lymphangiogenic drug as co-adjuvant therapy for rapamycin and thereby presenting as a potential new therapeutic approach for patients suffering from AML and most likely for patients suffering from LAM," stated Dr. Schuger.

AMLs, the most common benign heterogeneous kidney tumors, are composed of blood vessels, smooth muscle cells, and fat cells featuring mutations in genes of the TSC cell growth pathway. Although most AMLs are benign, some tumors spread to local lymph nodes and may impair kidney function or ultimately lead to life-threatening retroperitoneal hemorrhage. These tumors frequently occur in patients suffering from LAM, a rare lung disease of borderline malignancy. The LAM nodules, which are indistinguishable from AML [cells](#), tend to enlarge, proliferate, and cause cystic destruction of the lung leading to respiratory insufficiency.

**More information:** "Evidence Supporting a Lymphatic Endothelium Origin for Angiomyolipoma, a TSC2- Tumor Related to Lymphangioliomyomatosis," *The American Journal of Pathology*, [DOI:](#)

[10.1016/j.ajpath.2016.03.009](https://doi.org/10.1016/j.ajpath.2016.03.009)

Provided by Elsevier

Citation: New study lays groundwork for potential new anti-cancer therapy (2016, June 8)  
retrieved 20 April 2024 from

<https://medicalxpress.com/news/2016-06-groundwork-potential-anti-cancer-therapy.html>

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