

## RESEARCH WATCH

## Lymphoma

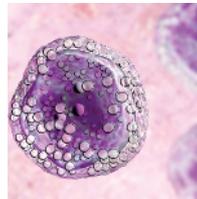
**Major Finding:** Lymphoma cells were more likely to take hold in gliotic central nervous systems (CNS) in mice.

**Mechanism:** Astrocytic CCL19 appeared responsible for retention of lymphoma cells in the CNS in mice and humans.

**Impact:** Age-related gliosis may partially explain the increased incidence of CNS lymphomas with age.

## LYMPHOMA CELLS ARE RETAINED IN GLIOTIC NERVOUS-SYSTEM TISSUE

Lymphomas may arise in or disseminate to the central nervous system (CNS), but how this occurs is unclear. O'Connor and colleagues developed a mouse model with high expression of lymphotoxins  $\alpha$  and  $\beta$  (LT $\alpha$  and LT $\beta$ ) in the CNS, resulting in chronic gliosis without severe damage to neurons or breakdown of the blood-brain barrier. This chronic gliosis conferred increased susceptibility to developing CNS lymphoma following intravenous injection of either of two types of neoplastic B cells. Although the expression of several leukocyte-specific cell-adhesion molecules (CAM) was upregulated in mice with CNS overexpression of LT $\alpha$  and LT $\beta$ , CAM upregulation alone was not sufficient to cause CNS lymphoma. Following injection of lymphoma cells, chronic gliosis was associated with an increase in parenchymal lymphoma cells. Though lymphoma cells also entered wild-type brain parenchyma, wild-type mice rarely developed CNS lymphoma. A possible explanation for this phenomenon is that lymphoma cells were more prone to being retained in the brain parenchyma



in mice with chronic gliosis. Astrocyte-generated CCL19 and lymphoma cell-expressed CCR7 were required for the retention of lymphoma cells in the gliotic mouse brains, and evidence of this mechanism was also observed in biopsies from patients with primary and secondary CNS lymphoma. In concordance with the facts that gliosis increases with age and that the average age of onset for primary CNS lymphoma is 65 years, larger B220<sup>+</sup> lesions developed in the brains of aged mice with gliosis than in younger mice following lymphoma-cell injection. Collectively, this work provides mechanistic insight into the relationship between aging-related gliosis and the development of CNS lymphoma and provides clues about possible risk factors for the disease. ■

O'Connor T, Zhou X, Kosla J, Adili A, Garcia Beccaria M, Kotsiliti E, et al. Age-related gliosis promotes central nervous system lymphoma through CCL19-mediated tumor cell retention. *Cancer Cell* 2019;36:250–67.E9.

## Liquid Biopsy

**Major finding:** Liquid biopsy outperforms single-lesion tumor biopsy in detecting heterogeneous resistance alterations.

**Approach:** Tumor biopsy and cfDNA were directly compared in a prospective cohort of patients with acquired drug resistance.

**Impact:** Liquid biopsy provides potential advantages in characterizing the full landscape of acquired resistance.

## COMPARISON OF cfDNA AND TISSUE BIOPSY SHOWS HETEROGENEITY IN RESISTANCE

Acquired resistance to antitumor targeted therapy is mediated by outgrowth of tumor subclones with resistance-associated genomic alterations. Such alterations within metastatic lesions are currently identified by genomic analysis of single-lesion tumor biopsies, but this analysis might underestimate tumor heterogeneity and not account for development of multiple resistant subclones arising concurrently in an individual patient. Liquid biopsy identifies circulating cell-free DNA (cfDNA) shed from tumor cells and thus would presumably better identify multiple resistance mechanisms than a single tumor tissue biopsy, but the two approaches have not yet been compared in a prospective manner. Parikh, Leshchiner, Elagina, and colleagues directly compared liquid biopsies with tissue biopsies in a prospective cohort of 42 patients with gastrointestinal cancers that progressed following targeted therapy. Genomic analysis of cfDNA identified at least one validated resistance alteration in 76% of patients; among them, 53% exhibited more than one resistance alteration. Overall, 78 different resistance alterations were found. Matched post-progression tumor biopsies, analyzed in 23 patients, identified resistance alterations in 11 of 23 (48%) patients, whereas cfDNA

analysis identified at least one resistance alteration in 20 of 23 (87%) patients. Only one of the 23 patients harbored a resistance alteration that was detected in tumor biopsy but not liquid biopsy. In 5 cases in which multiple biopsies or rapid autopsies were available, the presence of multiple resistance alterations across distinct metastatic lesions was confirmed. Although the number of patients analyzed was limited, these results demonstrate that acquired resistance to targeted therapy in gastrointestinal cancer is highly heterogeneous and that cfDNA from liquid biopsy can simultaneously identify multiple resistance alterations originating from different metastatic lesions in the same patient that a single tissue biopsy might not. These findings provide further evidence that incorporating liquid biopsy may be clinically valuable to detect acquired resistance mechanisms in patients whose cancers progress after targeted therapy. ■

Parikh AR, Leshchiner I, Elagina L, Goyal L, Levovitz C, Siravegna G, et al. Liquid versus tissue biopsy for detecting acquired resistance and tumor heterogeneity in gastrointestinal cancers. *Nat Med* 2019;25:1415–21.

# CANCER DISCOVERY

## Lymphoma Cells Are Retained in Gliotic Nervous-System Tissue

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