When mutations are found more commonly in cancerous tumors than in healthy tissue, they're often assumed to be cancer drivers. However, work by Buisson and colleagues suggests this isn’t always the case—mesoscale genomic features (those affecting dozens of bases but not vast stretches of the genome) may influence mutation frequency. A palindromic sequence can transiently form a hairpin with strength calculated using the number and identities of paired bases in its stem. Sequences estimated to be prone to forming strong hairpins had an increased frequency of APOBEC enzyme-signature mutations, and biochemical assays revealed that APOBEC3A was the only APOBEC enzyme with a substantial preference for hairpin substrates. In a whole-genome sequencing dataset from APOBEC+ tumors, a search for genomic locations with potential for forming hairpins revealed that stronger predicted stems were associated with increased APOBEC-signature mutations, and the location of the TpC dinucleotide (on which APOBECs act) in the loop was also important. According to in vitro assays in which sequence was varied systematically and analyses of sequencing data from APOBEC+ tumors, loop size and sequence context were also factors. Using this information, the authors developed a quantitative model for APOBEC-signature mutation likelihood based on noncoding areas of the genome, then applied it to mutations in coding regions from a cohort of 2,572 APOBEC+ patients who underwent whole-exome sequencing. Although there were APOBEC-signature mutations in cancer driver genes, they were not enriched in hairpins. In contrast, recurrent APOBEC-signature mutations in genes that are not strongly suspected to be cancer drivers were highly enriched in hairpins. For example, mutation hotspots in established cancer drivers PIK3CA and TP53 were only 1.2–1.9 times better substrates than average, whereas mutations in genes not validated as cancer drivers were often at optimal hairpin substrates (e.g., CL070, MROH2B, and NUP93 mutations were at 12–38 times better substrates). This illustrates that mutation frequency can be misleading and suggests that investigation of other mesoscale genomic features is needed.

**SOME MUTATIONAL HOTSPOTS MAY BE APOBEC3A-ASSOCIATED PASSENGERS**

Major Finding: Cancer-associated mutational hotspots may be created by APOBEC3As preference for certain structures.

Mechanism: The cytidine deaminase APOBEC3A preferentially mutates certain cytosines in DNA hairpins.

Impact: Caution is warranted in interpreting associations between cancers and specific mutational hotspots.

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**A KIR3DL2 ANTIBODY IS SAFE AND ACTIVE IN CUTANEOUS T-CELL LYMPHOMA**

Sézary syndrome is a particularly rare and aggressive subtype of cutaneous T-cell lymphoma with a median survival of only 2.5 to 4 years. KIR3DL2, a cell-surface protein, is often expressed in patients with T-cell lymphomas, including more than 85% of patients with Sézary syndrome. In a phase I clinical trial of IPH4102, a first-in-class monoclonal antibody to KIR3DL2, Bagot and colleagues showed that the drug is safe in T-cell lymphoma. IPH4102, which had previously been shown to be effective in mouse xenograft models and patient-derived NK and Sézary cells, is intended to target KIR3DL2-expressing cancer cells for antibody-dependent cytotoxicity and phagocytosis. The open-label trial enrolled 44 adult patients with relapsed or refractory primary cutaneous T-cell lymphoma who had undergone two or more previous systemic therapies. Of the patients, 35 (80%) had Sézary syndrome, 8 (18%) had mycosis fungoides, and 1 (2%) had primary cutaneous T-cell lymphoma. Based on preliminary dose-escalation experiments, which showed no dose-limiting toxicity, the maximum tested dose of 750 mg was used for cohort expansion. The most common side effects were peripheral edema and fatigue. The trial provided promising preliminary evidence of the drug’s efficacy: 16 (36%) of patients had a global overall response, and responses were observed in 15 of the 35 (43%) patients with Sézary syndrome. At data cutoff, the median duration of response in patients with Sézary syndrome was 13.8 months and the progression-free survival was 11.7 months. IPH4102 treatment was associated with an early reduction in the concentration of aberrant Sézary cells and circulating KIR3DL2-expressing CD4+ T cells, and biopsies obtained before and after treatment suggested that a ≥50% reduction of KIR3DL2-expressing skin cells or minimal residual disease in the blood was associated with response. A phase II study to confirm the activity of IPH4102 in Sézary syndrome and investigate its activity in other KIR3DL2-expressing T-cell lymphomas is ongoing.


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**T-cell Lymphoma**

**Major Finding:** KIR3DL2 antibody IPH4102 exhibits a favorable safety profile and preliminary evidence of efficacy.

**Mechanism:** The drug targets KIR3DL2, a cell-surface protein expressed in cutaneous T-cell lymphoma.

**Impact:** IPH4102 will undergo further trials to determine its efficacy in cutaneous T-cell lymphoma.

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Some Mutational Hotspots May Be APOBEC3A-Associated Passengers


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