CANCER

Detection of mouse viruses in patient-derived xenografts

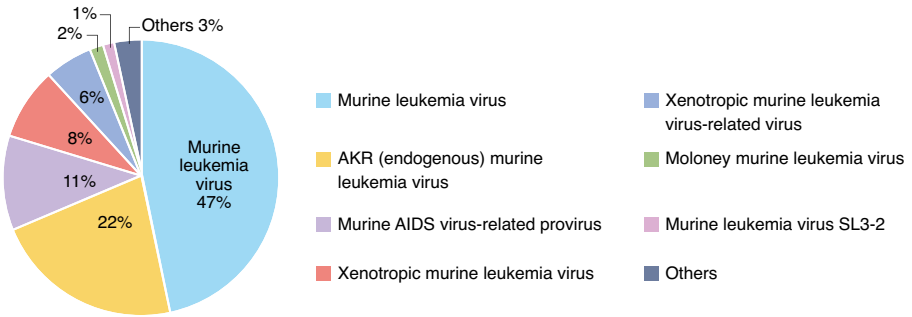
Yuan, Z. et al. *Nat. Commun.* **12**, 2031 (2021)

Establishing an appropriate preclinical model is critical for translational cancer research. Patient-derived xenografts (PDX) models are created by implanting tumor tissue from a donor patient into immunocompromised mice, which preserves both cell–cell interactions and tumor microenvironment. PDX models are considered to be a more faithful representation of human cancer than 'simpler' models derived from cancer cell lines, and preclinical studies are increasingly relying on these models for drug screening, biomarker discovery and evaluation of personalized therapy.

There has however been debate about the reliability of PDX models. For example, a 2017 study suggested that PDX can diverge genetically from the patient's tumor throughout passaging by developing copy number alterations that affect how PDX respond to cancer therapies. A recent study reached an opposite conclusion and showed strong parallels between the genome of PDX and the tumors from which they were established.

Now, a study published in *Nature Communications* raises new concerns about the use of PDX for preclinical cancer research by providing evidence that PDX samples are infected with murine viruses. Viral infection could cause discrepancies between the patient sample and PDX and limit the translational validity of PDX models.

Previous studies had already reported the presence of murine viruses in PDX tumors, but these studies analyzed few samples (<50). Here, Zihao Yuan and colleagues at UT Health Science Center at Houston analyzed RNA-seq data from 184 datasets generated from human-derived PDX tumors (including PDX models of glioblastoma, as well as bladder, breast, colorectal, lung, ovarian and pancreatic cancers) and compared them to corresponding primary tumors that had not been exposed to mice or murine viruses. They identified murine viral sequence reads in 170 of the 184 PDX samples. Approximately half of the identified viruses were murine leukemia virus; others included various endogenous murine retroviruses and murine viruses, such as AIDS virus-related provirus and AKT8 retrovirus, which had not been reported in PDX tumors before.



Major categories of murine virus as identified by sequence reads from all PDX cancer samples. Adapted from Yuan et al (2021). Springer Nature.

Given that PDX tumors are implanted into host mice, the detected murine viral reads could be the result of mouse stromal cells contaminating the human tissue. "RNA-seq data generated from PDX tumors capture expressed RNA from PDX tumors and viruses that could infect murine stromal cells and PDX tumor cells. Unfortunately, in a typical RNA-seq data analysis, sequencing reads are mapped to the human genome to evaluate expression levels of human genes or genome DNA variations. Unmapped reads—the 'dark matter' of the sequencing data that most likely include mouse stromal cells and viral sequence reads—are disregarded," explain the investigators in their report.

Yuan et al. analyzed the "dark matter" of the sequencing data to identify the source of the viruses. Their findings indicated that even though PDX are contaminated with stromal cells that produce viruses, PDX tumor cells were also a source for the murine viruses.

The investigators also used the available data to evaluate the effects of viral infection on PDX gene expression profiles. That analysis revealed significant differences in gene expression between samples with low and high murine virus loads, with differentially expressed genes that were are enriched with ontology terms related to immune regulation and important signaling and disease pathways. As an example, *CD80* was downregulated in PDX tumors with high viral load; given the essential roles of this gene in immune therapy deployment, viral infection could be a confounding variable in experiments testing the efficacy of immune therapy in PDX models.

The study also reveals the presence of sequence reads containing both murine viral genome and human sequences, which suggests that murine retroviruses can integrate their genome into their host genome. "Our results also indicate the need for more quality control in experiments using tissues of human origin in murine xenografts. For such experiments, conventional sanitation and pathogen control, as well as risk assessment of viral infection, should be in place," write the investigators. "Such practices could have a profound impact on the success of cancer drug development on PDX models," they conclude.

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