

# Toward a Unified Theory of Why Young People Develop Cancer

Alex Kentsis

Tow Center for Developmental Oncology, Sloan Kettering Institute and Department of Pediatrics, Weill Medical College of Cornell University and Memorial Sloan Kettering Cancer Center, New York, New York 10065, USA

Correspondence: kentsisresearchgroup@gmail.com

Epidemiologic and genetic studies have now defined specific patterns of incidence and distinct molecular features of cancers in young versus aging people. Here, I review a general framework for the causes of cancer in children and young adults by relating somatic genetic mosaicism and developmental tissue mutagenesis. This framework suggests how aging-associated cancers such as carcinomas, glioblastomas, and myelodysplastic leukemias are causally distinct from cancers that predominantly affect children and young adults, including lymphoblastic and myeloid leukemias, sarcomas, neuroblastomas, medulloblastomas, and other developmental cancers. I discuss the oncogenic activities of known developmental mutators RAG1/2, AID, and PGBD5, and describe strategies needed to define missing developmental causes of young-onset cancers. Thus, a precise understanding of the mechanisms of tissue-specific somatic mosaicism, developmental mutators, and their control by human genetic variation and environmental exposures is needed for improved strategies for cancer screening, prevention, and treatment.

History of science is rich with diverse theories about the origins of human cancer. Around 400 BCE, Hippocrates favored the humoral cause of cancer due to the excess of black bile (Diamantopoulos 1996). Once human anatomy was initially defined in the 1700s with its notable lack of evidence for black bile, Stahl and Hoffman proposed that cancer is caused by the degeneration of lymph nodes. With the advent of microscopy in the nineteenth century, Müller and later Virchow showed that cancer is instead a disease of cells (DeVita and Rosenberg 2012). This is indeed the case, but what causes cancer?

By the early twentieth century, oncogenic viruses were among the first proven causes of cancer in vertebrates (Krump and You 2018). Many

also recognized abnormal genomes of cancer cells, beginning with the seminal studies of Hansemann and Boveri in the early twentieth century, who documented the abnormal numbers and appearance of chromosomes in cancer cells (Bignold et al. 2006). It was not until the 1960s that chromosomal abnormalities were linked to mutational oncogene activation as the cause of cancer (Fröhling and Döhner 2008).

## SOMATIC MOSAICISM IN CANCER DEVELOPMENT

Current understanding of how cancer develops is fundamentally based on a multistage mutation model. Originally introduced by Armitage and

## A. Kentsis

Doll, the multistage model explains that as people age, the risk of cancer increases due to the accumulation of genetic mutations in cells (Frank 2007). These mutations can at some frequency involve genes that control cell growth and development, originally termed oncogenes and tumor suppressor genes. When specific mutations in these genes occur together, they can transform healthy cells into fully malignant cancerous ones, as documented by numerous engineered cellular and animal model systems.

According to this model, certain factors can accelerate the development of cancer. These include exposure to mutagens that can damage DNA and lead to somatic mutations, or inheriting genetic traits (alleles) that make cells less capable of repairing DNA damage, maintaining genomic integrity, or regulating cell growth and division. In older adults, the majority of cancers are believed to arise from random and stochastic mutations that accumulate over time in tissues as byproducts of continuous cell division and regeneration (Tomasetti and Vogelstein 2015; Tomasetti et al. 2017). This gradual buildup of mutations is thought to contribute to the higher cancer risk seen with increasing age.

Indeed, numerous recent studies have documented somatic genetic mosaicism in various healthy tissues, often involving somatic mutations of known tumor suppressor genes, without overt cancer development (Martincorena et al. 2015; Blokzijl et al. 2016; Lee-Six et al. 2019; Solís-Moruno et al. 2023). These precancerous cells are thought to provide a reservoir of cells somatically predisposed to malignant transformation and clinical cancer progression (Kakiuchi and Ogawa 2021).

This framework offers a cogent mechanism for the development of cancers in children and young adults. In fact, several recent studies of inferred timing of somatic mutations in adult-onset cancers have concluded that the founding genetic lesions often occurred during embryogenesis or early childhood (Gerstung et al. 2020; Pareja et al. 2022; Williams et al. 2022). During development, in a particularly susceptible cell type or state, as few as one mutation affecting a key tumor suppressor or oncogene, blocking cell differentiation, could ultimately lead to malig-

nant transformation. Thus, premature somatic mosaicism, accelerated by inherited cancer-predisposing alleles or environmental exposure to mutagens, is the de facto cause of young-onset cancer in children and young adults.

## DEVELOPMENTAL MUTAGENESIS

However, there are several pieces of evidence that suggest that premature somatic mosaicism cannot be the only cause. First, numerous genomic surveys of the somatically mutated genes in aging-associated cancers in older adults (carcinomas, glioblastomas, myelodysplastic leukemias) versus cancers that predominantly affect children and young adults (lymphoblastic leukemias, sarcomas, neuroblastomas, medulloblastomas) have documented extensive divergence of the specific oncogenes and tumor suppressor genes mutated in the aging- and young-onset cancers (Chatsirisupachai et al. 2021; Li et al. 2022; Wang et al. 2022). For example, aging-associated cancers in older adults almost always involve oncogenic somatic mutations of *TP53*, whereas somatic tumor *TP53* mutations are vanishingly rare at diagnosis in children (Robles et al. 2016; Gröbner et al. 2018; Ma et al. 2018). In addition, cancer genomes in older adults have very high rates of single or dinucleotide substitutions, often termed mutational burden, whereas cancers from children and young adults have somatic nucleotide mutation rates that are similar to their corresponding healthy tissues (Thatikonda et al. 2023). Instead, young-onset cancers have increased rates of genome rearrangements, including deletions, translocations, and other complex DNA structural variants (Gröbner et al. 2018; Ma et al. 2018).

In addition to these fundamentally distinct molecular features of aging-associated versus young-onset cancers, epidemiologic studies of the incidence of different types of human cancer have also documented pronounced differences in the age-dependence of these cancers (for review, see Kentsis 2020; Kentsis and Frank 2020). For example, most adenocarcinomas, such as those affecting the colon and lung, exhibit monotonically increasing incidence with increasing age. In contrast, cancers that tend to affect children and

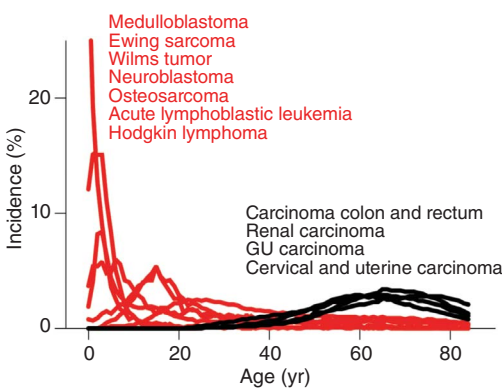
young adults, including lymphoblastic leukemias, Hodgkin lymphomas, sarcomas, neuroblastomas, and medulloblastomas, exhibit distinct peaks of incidence, as evident from the analysis of the surveillance, epidemiology, and end results (SEER) program data (Fig. 1). Thus, specific molecular features and age-dependent incidence of young-onset cancers must result from distinct primary causes from those leading to aging-associated cancers in older adults.

The occurrence of specific cancer types in childhood and young adulthood can be attributed to two nonmutually exclusive primary mechanisms. First, the presence of stem or progenitor cells with impaired DNA damage repair capabilities during normal tissue development, coupled with inherent DNA damage from cell division, can cause somatic mutations of essential oncogenes and tumor suppressor genes, leading to cancer initiation. Alternatively, somatic oncogenic mutations can be induced by developmental mutators including nucleases and other cellular processes that induce DNA mutations that are divergent from their healthy physiologic substrates. These mechanisms could lead to different types of somatic mutations and distinct genomic signatures in the resulting young-onset tumors. This developmental mutator mechanism is distinct from premature somatic mosaicism, a process primarily linked to the onset of

aging-related cancers in older individuals (see above).

The distinction between developmental mutators and somatic mosaicism as causes of young-onset cancers may also have a significant evolutionary consequence. Until the advent of modern medicine, virtually all cases of human cancer were lethal. This implies that the biological mechanisms leading to cancer in young individuals during their reproductive years are subject to intense negative evolutionary pressure. This pressure results in both affected individuals and the specific genetic variants they possess being eliminated from the population. Thus, premature somatic mosaicism may be thought of as an accidental cause of a lethal disease, since most of its biological causes affect older adults post their reproductive age. In contrast, developmental mutators, by virtue of affecting children and causing young-onset cancer incidence, must also have essential developmental functions, which thereby can offset the evolutionary cost of their potential to cause cancer.

For example, the most common childhood cancer is acute lymphoblastic leukemia (ALL). ALL is frequently caused by specific chromosomal translocations and deletions that dysregulate developmental transcription factors and other regulators of cell growth and development (Iacobucci and Mullighan 2017). In many cases, DNA breakpoints of these chromosomal translocations and deletions involve specific sequences that are the substrates of the RAG1/2 DNA recombinase (Mullighan et al. 2008; Paemmanuil et al. 2014). Indeed, deficiency of RAG1/2 in engineered mouse models prevents leukemia development (Swaminathan et al. 2015). Normal lymphocyte development also involves activation of the APOBEC-family deaminase AID, which also induces somatic mutations that are characteristically found in many cases of lymphomas, another common blood cancer (Gu et al. 2012; Burns et al. 2013; Pettersen et al. 2015). Remarkably, the expression of RAG1/2 and its stereotypical somatic DNA rearrangements have also been detected in subsets of childhood acute myeloid leukemia (AML) (Boehm et al. 1987; Dyer et al. 1991; van Dongen et al. 1992; McNeer et al. 2019).



**Figure 1.** Age-dependent incidence of (red) young-onset versus (black) aging cancers. (GU) Genitourinary. (Figure based on data acquired from the SEER database of 8,662,369 malignant cases spanning 1973–2014.)

## A. Kentsis

Thus, RAG1/2 and AID are the primary developmental mutators for many blood cancers affecting children and young adults. This evolutionary cost of causing young-onset cancers is offset by the fundamental functions of RAG1/2 and AID in the healthy development of adaptive immunity, an essential evolutionary adaptation that prevents infectious disease in all vertebrate animals and humans. Similar evolutionary trade-offs have been extensively documented for many physiologic functions in diverse living organisms (Haldane and Dronamraju 1990).

While RAG1/2 and AID likely induce cancer-initiating mutations in many young-onset blood cancers, they are not expressed beyond the hematopoietic lineage, and specifically not in other cancers that characteristically affect children and young adults. Thus, additional developmental mutators must exist. Recently, PGBD5, another evolutionarily conserved nuclease with mutagenic activity in human cells, was found to be expressed in the majority of solid tumors that affect children and young adults, including various sarcomas, medulloblastomas, and neuroblastomas (Henssen and Kentsis 2018). In rhabdoid tumors, PGBD5 has been found to mediate sequence-specific somatic deletions and other DNA rearrangements, including those of the essential rhabdoid tumor suppressor gene *SMARCB1* (Henssen and Kentsis 2018). In recent studies, similar mutagenic activity of PGBD5 was also found in medulloblastomas, which is the most common childhood brain tumor (Yamada et al. 2024). In fact, most *Pgbd5*-deficient mice are protected from medulloblastoma-induced mutations of *Ptch1* and *Smo*, which are penetrant tumor suppressor and oncogene mutations in human medulloblastomas. Remarkably, PGBD5 is deeply evolutionarily conserved among vertebrates and is required for normal brain development, as its inherited deficiency has recently been found to cause a human intellectual disability syndrome (Jubierre Zapater et al. 2023).

Thus, as RAG1/2 is the developmental mutator nuclease for childhood blood cancers, PGBD5 appears to be a mutator nuclease for a subset of childhood solid tumors. While inflammatory signaling appears to regulate the activity of RAG1/2 in developing blood progen-

itor cells, consistent with the epidemiologic link between the incidence of ALL and infectious exposures in childhood, the molecular mechanisms and biological processes that dysregulate RAG1/2 and PGBD5 to cause oncogenic mutations and cell transformation are currently unknown.

## TOWARD INTEGRATIVE MODELS OF CANCER DEVELOPMENT

Many tumors that affect children and young adults do not express RAG1/2, AID, or PGBD5. These distinct childhood cancers, such as astrocytomas, for example, exhibit distinct somatic mutational signatures in agreement with the developmental mutator causal model. To the extent that the expression of RAG1/2, AID, and PGBD5 is ultimately related to the specific cell lineages from which developmental tumors originate, additional developmental mutators in specific young-onset cancers may be found through the study of developmental nucleases and other developmental molecular processes that act on DNA (Kentsis and Frank 2020).

The developmental nuclease-enzyme hypothesis is especially attractive for developmental cancers with distinct mutational features. For example, mixed lineage leukemias have distinct chromosomal translocations, with topoisomerase 2 implicated in the induction of these oncogenic DNA rearrangements (Sung et al. 2006; Cowell et al. 2012). However, the mechanisms by which topoisomerase 2 or another enzyme that generates these developmental oncogenic mutations are currently not well defined. Similarly, Wilms tumors, the most common kidney tumors in children, have specific patterns of somatic deletions and duplications (Gadd et al. 2017). The causes of this distinct and extensive somatic mutagenesis in children without known genetic predisposition or genomic instability are currently unknown.

It is also possible that developmental tumorigenesis may involve heritable epigenetic defects that lead to malignant transformation, without primary somatic mutations. One can envision that developmental induction of specific metabolites or other forms of epigenetic dysregulation

can lead to heritable changes in gene expression and cell transformation. Remarkably, recent studies have found extensive somatic DNA imprinting mosaicism in children with sporadic Wilms tumors and hepatoblastomas (Coorens et al. 2019; Fiala et al. 2020). Similarly, distinct subsets of ependymomas currently lack known pathogenic DNA mutations (Yamaguchi et al. 2023). The causal developmental processes for such epigenetic tumorigenesis require further study.

Finally, the premature somatic mosaicism and developmental mutator causes of young-onset cancers are not necessarily mutually exclusive. First, the two processes can co-occur within the same individual, tissue, and cell of origin. Second, to the extent that most human cancers are caused by multiple somatic mutations, distinct genetic causes can cooperate in their induction. Lastly, the epidemiologic variability of the incidence of distinct cancers among different groups of individuals means that differences in environmental exposure and/or germline genetic variation can contribute to cancer risk. A precise understanding of the mechanisms of tissue-specific somatic mosaicism, developmental mutators, and human genetic variation and exposures is required for improved strategies for cancer screening, prevention, and treatment.

## ACKNOWLEDGMENTS

I thank Alejandro Gutierrez for critical reading of the early draft of this manuscript, Helen Mueller, Makiko Yamada, and Damon Reed for suggestions, and Gabriella Casalena for help with figure design.

## REFERENCES

Bignold LP, Coghlan BL, Jersmann HP. 2006. Hansemann, Boveri, chromosomes and the gametogenesis-related theories of tumours. *Cell Biol Int* **30**: 640–644. doi:10.1016/j.cellbi.2006.04.002

Blokzijl F, de Ligt J, Jager M, Sasselli V, Roerink S, Sasaki N, Huch M, Boymans S, Kuijk E, Prins P, et al. 2016. Tissue-specific mutation accumulation in human adult stem cells during life. *Nature* **538**: 260–264. doi:10.1038/nature19768

Boehm TL, Werle A, Drahovsky D. 1987. Immunoglobulin heavy chain and T-cell receptor  $\gamma$  and  $\beta$  chain gene rear-

rangements in acute myeloid leukemias. *Mol Biol Med* **4**: 51–62.

Burns MB, Temiz NA, Harris RS. 2013. Evidence for APO-BEC3B mutagenesis in multiple human cancers. *Nat Genet* **45**: 977–983. doi:10.1038/ng.2701

Chatsirisupachai K, Lesluyes T, Paraoan L, Van Loo P, de Magalhães JP. 2021. An integrative analysis of the age-associated multi-omic landscape across cancers. *Nat Commun* **12**: 2345. doi:10.1038/s41467-021-22560-y

Coorens THH, Treger TD, Al-Saadi R, Moore L, Tran MGB, Mitchell TJ, Tugnait S, Thevanesan C, Young MD, Oliver TRW, et al. 2019. Embryonal precursors of Wilms tumor. *Science* **366**: 1247–1251. doi:10.1126/science.aax1323

Cowell IG, Sondka Z, Smith K, Lee KC, Manville CM, Sidorcuk-Lesthuruge M, Rance HA, Padgett K, Jackson GH, Adachi N, et al. 2012. Model for *MLL* translocations in therapy-related leukemia involving topoisomerase II $\beta$ -mediated DNA strand breaks and gene proximity. *Proc Natl Acad Sci* **109**: 8989–8994. doi:10.1073/pnas.1204406109

DeVita VT Jr, Rosenberg SA. 2012. Two hundred years of cancer research. *N Engl J Med* **366**: 2207–2214. doi:10.1056/NEJMr1204479

Diamandopoulos GT. 1996. Cancer: an historical perspective. *Anticancer Res* **16**: 1595–1602.

Dyer MJ, Hoyle CF, Rees JK, Marcus RE. 1991. T-cell receptor and immunoglobulin gene rearrangements in acute myeloid and undifferentiated leukemias of adults: correlation with weak surface expression of CD45 and CDw52 antigens. *Leuk Lymphoma* **3**: 257–265. doi:10.3109/10428199109107913

Fiala EM, Ortiz MV, Kennedy JA, Glodzik D, Fleischut MH, Duffy KA, Hathaway ER, Heaton T, Gerstle JT, Steinherz P, et al. 2020. 11p15.5 epimutations in children with Wilms tumor and hepatoblastoma detected in peripheral blood. *Cancer* **126**: 3114–3121. doi:10.1002/cncr.32907

Frank SA. 2007. *Dynamics of cancer: incidence, inheritance, and evolution*. Princeton University Press, Princeton, NJ.

Fröhling S, Döhner H. 2008. Chromosomal abnormalities in cancer. *N Engl J Med* **359**: 722–734. doi:10.1056/NEJMr0803109

Gadd S, Huff V, Walz AL, Ooms AHAG, Armstrong AE, Gerhard DS, Smith MA, Auvil JMG, Meerzaman D, Chen QR, et al. 2017. A children's oncology group and TARGET initiative exploring the genetic landscape of Wilms tumor. *Nat Genet* **49**: 1487–1494. doi:10.1038/ng.3940

Gerstung M, Jolly C, Leshchiner I, Drento SC, Gonzalez S, Rosebrock D, Mitchell TJ, Rubanova Y, Anur P, Yu K, et al. 2020. The evolutionary history of 2,658 cancers. *Nature* **578**: 122–128. doi:10.1038/s41586-019-1907-7

Gröbner SN, Worst BC, Weischenfeldt J, Buchhalter I, Kleinheinz K, Rudneva VA, Johann PD, Balasubramanian GP, Segura-Wang M, Brabetz S, et al. 2018. The landscape of genomic alterations across childhood cancers. *Nature* **555**: 321–327. doi:10.1038/nature25480

Gu X, Shivarov V, Strout MP. 2012. The role of activation-induced cytidine deaminase in lymphomagenesis. *Curr Opin Hematol* **19**: 292–298. doi:10.1097/MOH.0b013e328353da3a

## A. Kentsis

- Haldane JBS, Dronamraju KR. 1990. *Selected genetic papers of J.B.S. Haldane*. Garland, New York.
- Henssen AG, Kentsis A. 2018. Emerging functions of DNA transposases and oncogenic mutators in childhood cancer development. *JCI Insight* **3**: e123172. doi:10.1172/jci.insight.123172
- Iacobucci I, Mullighan CG. 2017. Genetic basis of acute lymphoblastic leukemia. *J Clin Oncol* **35**: 975–983. doi:10.1200/JCO.2016.70.7836
- Jubierre Zapater LJ, Rodriguez-Fos E, Planas-Felix M, Lewis S, Cameron D, Demarest P, Nabila A, Zhao J, Bergin P, Reed C, et al. 2023. A transposase-derived gene required for human brain development. bioRxiv doi:10.1101/2023.04.28.538770
- Kakiuchi N, Ogawa S. 2021. Clonal expansion in non-cancer tissues. *Nat Rev Cancer* **21**: 239–256. doi:10.1038/s41568-021-00335-3
- Kentsis A. 2020. Why do young people get cancer? *Pediatr Blood Cancer* **67**: e28335. doi:10.1002/psc.28335
- Kentsis A, Frank SA. 2020. Developmental mutators and early onset cancer. *Front Pediatr* **8**: 189. doi:10.3389/fped.2020.00189
- Krump NA, You J. 2018. Molecular mechanisms of viral oncogenesis in humans. *Nat Rev Microbiol* **16**: 684–698. doi:10.1038/s41579-018-0064-6
- Lee-Six H, Olafsson S, Ellis P, Osborne RJ, Sanders MA, Moore L, Georgakopoulos N, Torrente F, Noorani A, Goddard M, et al. 2019. The landscape of somatic mutation in normal colorectal epithelial cells. *Nature* **574**: 532–537. doi:10.1038/s41586-019-1672-7
- Li CH, Haider S, Boutros PC. 2022. Age influences on the molecular presentation of tumours. *Nat Commun* **13**: 208. doi:10.1038/s41467-021-27889-y
- Ma X, Liu Y, Liu Y, Alexandrov LB, Edmonson MN, Gawad C, Zhou X, Li Y, Rusch MC, Easton J, et al. 2018. Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. *Nature* **555**: 371–376. doi:10.1038/nature25795
- Martincorena I, Roshan A, Gerstung M, Ellis P, Van Loo P, McLaren S, Wedge DC, Fullam A, Alexandrov LB, Tubio JM, et al. 2015. Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. *Science* **348**: 880–886. doi:10.1126/science.aaa6806
- McNeer NA, Philip J, Geiger H, Ries RE, Lavallée VP, Walsh M, Shah M, Arora K, Emde AK, Robine N, et al. 2019. Genetic mechanisms of primary chemotherapy resistance in pediatric acute myeloid leukemia. *Leukemia* **33**: 1934–1943. doi:10.1038/s41375-019-0402-3
- Mullighan CG, Phillips LA, Su X, Ma J, Miller CB, Shurtleff SA, Downing JR. 2008. Genomic analysis of the clonal origins of relapsed acute lymphoblastic leukemia. *Science* **322**: 1377–1380. doi:10.1126/science.1164266
- Papaemmanuil E, Rapado I, Li Y, Potter NE, Wedge DC, Tubio J, Alexandrov LB, Van Loo P, Cooke SL, Marshall J, et al. 2014. RAG-mediated recombination is the predominant driver of oncogenic rearrangement in ETV6-RUNX1 acute lymphoblastic leukemia. *Nat Genet* **46**: 116–125. doi:10.1038/ng.2874
- Pareja F, Ptashkin RN, Brown DN, Derakhshan F, Selenica P, da Silva EM, Gazzo AM, Da Cruz Paula A, Breen K, Shen R, et al. 2022. Cancer-causative mutations occurring in early embryogenesis. *Cancer Discov* **12**: 949–957. doi:10.1158/2159-8290.CD-21-1110
- Pettersen HS, Galashevskaya A, Doseth B, Sousa MM, Sarno A, Visnes T, Aas PA, Liabakk NB, Slupphaug G, Sætrum P, et al. 2015. AID expression in B-cell lymphomas causes accumulation of genomic uracil and a distinct AID mutational signature. *DNA Repair (Amst)* **25**: 60–71. doi:10.1016/j.dnarep.2014.11.006
- Robles AI, Jen J, Harris CC. 2016. Clinical outcomes of TP53 mutations in cancers. *Cold Spring Harb Perspect Med* **6**: a026294. doi:10.1101/cshperspect.a026294
- Solis-Moruno M, Batlle-Masó L, Bonet N, Aróstegui JI, Casals F. 2023. Somatic genetic variation in healthy tissue and non-cancer diseases. *Eur J Hum Genet* **31**: 48–54. doi:10.1038/s41431-022-01213-8
- Sung PA, Libura J, Richardson C. 2006. Etoposide and illegitimate DNA double-strand break repair in the generation of MLL translocations: new insights and new questions. *DNA Repair (Amst)* **5**: 1109–1118. doi:10.1016/j.dnarep.2006.05.018
- Swaminathan S, Klemm L, Park E, Papaemmanuil E, Ford A, Kweon SM, Trageser D, Hasselfeld B, Henke N, Mooster J, et al. 2015. Mechanisms of clonal evolution in childhood acute lymphoblastic leukemia. *Nat Immunol* **16**: 766–774. doi:10.1038/ni.3160
- Thatikonda V, Islam SMA, Autry RJ, Jones BC, Gröbner SN, Warsow G, Hutter B, Huebschmann D, Fröhling S, Kool M, et al. 2023. Comprehensive analysis of mutational signatures reveals distinct patterns and molecular processes across 27 pediatric cancers. *Nat Cancer* **4**: 276–289. doi:10.1038/s43018-022-00509-4
- Tomasetti C, Vogelstein B. 2015. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* **347**: 78–81. doi:10.1126/science.1260825
- Tomasetti C, Li L, Vogelstein B. 2017. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science* **355**: 1330–1334. doi:10.1126/science.aaf9011
- van Dongen JJ, Breit TM, Adriaansen HJ, Beishuizen A, Hooijkaas H. 1992. Detection of minimal residual disease in acute leukemia by immunological marker analysis and polymerase chain reaction. *Leukemia* **6**: 47–59.
- Wang X, Langevin AM, Houghton PJ, Zheng S. 2022. Genomic disparities between cancers in adolescent and young adults and in older adults. *Nat Commun* **13**: 7223. doi:10.1038/s41467-022-34959-2
- Williams N, Lee J, Mitchell E, Moore L, Baxter EJ, Hewinson J, Dawson KJ, Menzies A, Godfrey AL, Green AR, et al. 2022. Life histories of myeloproliferative neoplasms inferred from phylogenies. *Nature* **602**: 162–168. doi:10.1038/s41586-021-04312-6
- Yamada M, Keller RR, Gutierrez RL, Cameron D, Suzuki H, Sanghrajka R, Vaynshteyn J, Gerwin J, Maura F, Hooper W, et al. 2024. Childhood cancer mutagenesis caused by transposase-derived PGBD5. *Sci Adv* **10**: 1–16. doi:10.1126/sciadv.adn4649
- Yamaguchi J, Ohka F, Motomura K, Saito R. 2023. Latest classification of ependymoma in the molecular era and advances in its treatment: a review. *Jpn J Clin Oncol* **53**: 653–663. doi:10.1093/jjco/hyad056