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Review article

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Cancers make their own luck: theories of cancer origins

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Abstract

Cancer has been a leading cause of death for decades. This dismal statistic has increased efforts to prevent the disease or to detect it early, when treatment is less invasive, relatively inexpensive and more likely to cure. But precisely how tissues are transformed continues to provoke controversy and debate, hindering cancer prevention and early intervention strategies. Various theories of cancer origins have emerged, including the suggestion that it is 'bad luck': the inevitable consequence of random mutations in proliferating stem cells. In this Review, we discuss the principal theories of cancer origins and the relative importance of the factors that underpin them. The body of available evidence suggests that developing and ageing tissues 'walk a tightrope', retaining adequate levels of cell plasticity to generate and maintain tissues while avoiding overstepping into transformation. Rather than viewing cancer as 'bad luck', understanding the complex choreography of cell intrinsic and extrinsic factors that characterize transformation holds promise to discover effective new ways to prevent, detect and stop cancer before it becomes incurable.

Sections

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Introduction

The successful treatment of any disease requires an understanding of the biology at work in diseased tissues. During the nineteenth and early twentieth centuries, infectious diseases were the leading cause of death[1,2] (Fig. 1). Early recognition that these diseases might be prevented through appropriate quarantine and sanitation[3], followed by the discovery of bacteria and viruses as their causative agents, inspired basic research[4], prevention[5] and targeted chemotherapy programmes[6,7]. This evolution in thinking brought about a fundamental change in our understanding, prevention and treatment of infection, and thereby a dramatic decline in morbidity and mortality (Fig. 1). Public health measures and the development of vaccines have been central to this success, preventing some infections from ever taking hold[8,9].

As infection control improved through the first half of the twentieth century, the evolving practice of modern medicine was applied to cancer, which had emerged as a major killer (Fig. 1). The discovery of chemicals that could kill rapidly dividing cells launched the field of cancer chemotherapy[10,11], whereas the understanding of oncogenes and crosstalk between cancer and the immune system has yielded effective molecule-targeted therapies[12] and immunotherapies[13,14], respectively.

Despite these advances, cancer remains a leading cause of death by disease. Every year, more than 19 million people are diagnosed with cancer and 10 million die of the disease, accounting for one in six deaths globally[15]. Two thirds of these deaths occur in lower and middle-income countries where cancer is often diagnosed late and access to treatment is limited[15]. Even in relatively developed countries, more than one third of patients diagnosed with cancer present as emergency cases with relatively late-stage disease and a significantly increased risk of dying within 12 months[16]. The annual global cancer burden is expected to rise to more than 28 million cases by 2040, with a larger increase in transitioning countries (from 64% to 95%) than in transitioned countries (from 32% to 56%)[15]. These dismal statistics have prompted worldwide calls to reduce cancer mortality by a third within the next decade[17–19]. Increasing focus is being placed on detecting and treating cancer, or its precursors, as early as possible in the belief that this approach will dramatically increase patient survival while decreasing the invasiveness, cost and side effects of treatment[20,21].

Achieving this ambition will require a sea change in the way we study and manage cancer. Similar to the control of infectious disease, the greatest reductions in cancer mortality have been achieved through epidemiological research and primary prevention measures including tobacco control[22], regulating occupational carcinogen exposure[23] and vaccines[24,25]. Although much of this success has been achieved without detailed knowledge of the biology of cancer origins, further progress will require an evolution of our approach to the challenge of cancer. At least half of all cancers are still thought to be preventable[26], yet the majority of cancer research funding is invested in late-stage disease. Concerted, multidisciplinary research efforts engaging basic, epidemiological and clinical researchers armed with a better understanding of cancer origins will be required if we are to invent effective strategies that prevent cancer or detect and treat it early.

In this Review, we discuss the principal theories of cancer origins and the relative contribution of intrinsic and extrinsic factors to malignancy. It is envisaged that a better understanding of these processes will significantly accelerate our ability to diagnose cancer early, and treat it more precisely, when the disease is easier to control with less expensive and relatively non-toxic treatments.

Theories of cancer origins

Differences in exposure to risk factors and life expectancy result in global heterogeneity in the leading cancer types; but cancers are not distributed randomly across the body. This is most apparent in the comparison of paediatric[27] and adult[19] malignancies (Fig. 2). Paediatric malignancies are relatively rare (1 in 440 children)[27,28], initiate during embryogenesis predominantly within ectodermal (for example, brain tumours) and mesodermal (for example, haematological malignancies) lineages, and have a relatively low mutational burden. Conversely, one in two adults develop cancer with a relatively high mutational burden, and almost entirely within epithelial tissues after the sixth decade of life[19]. These patterns suggest strongly that cancer is not a random process but one dictated by reproducible determinants in developing and ageing tissues.

Although the incidence and age of onset of many cancer types are well documented, our understanding of how cancers arise continues to provoke debate (Fig. 3 and Box 1). The observation that cancer incidence increases with age has been explained by the somatic mutation theory of cancer. First proposed almost 100 years ago, this theory posits that cancers arise in proliferating cell lineages that acquire six or seven 'factors' (now believed to be DNA mutations) during life[29–32]. But certain observations do not fit this theory, including spontaneous or hormone-driven regression of paediatric and adult cancers[33,34], normalization of malignant teratomas injected into blastocysts[35] and evidence that many carcinogens do not damage DNA[36,37]. Therefore, Soto and Sonnenschein[38] proposed an alternative tissue organization field theory of cancer (Fig. 3). The tissue organization field theory proposes that whole tissues are the target of carcinogens, disturbing the biophysical and biomechanical communication between the parenchyma and the mesenchyme or stroma. As a consequence, the proliferation and motility restraints imposed by normal tissue architecture are lost, inducing progressive metaplasia, dysplasia and carcinoma. Recently, two additional theories have been proposed — the bad luck[39] and ground state[40] theories — that draw on concepts underpinning both the somatic mutation and tissue organization field theories (Fig. 3).

The bad luck theory

Tomasetti and colleagues[39,41] proposed a model in which random mistakes made during DNA replication in stem cells (R-mutations) result in the inevitable propagation of mutant clones leading to cancer (Fig. 3). This model distinguishes R-mutations from those that are heritable (H-mutations) or caused by environmental carcinogens (E-mutations). By comparing the incidence of 17 human cancer types reported in 423 cancer registries across 69 countries with estimated rates of stem cell division in the corresponding host tissues, the authors calculated that as many as two thirds of cancer-causing mutations are R-mutations.

Although similar to the somatic mutation theory, the bad luck theory — so called because R-mutations and stem cell divisions are an inevitable characteristic of tissues — is important as it provides a conceptual framework to understand the relative contributions of H, E and R-factors to cancer risk.

But elements of the bad luck theory are problematic. It is well established that cancer risk varies temporarily and geographically in a manner that cannot be attributed merely to the chance mutation of dividing stem cells[42]. Furthermore, the assumption that cancer risk is dictated entirely by the number of stem cell divisions throughout life does not adequately account for other cell intrinsic (for example, epigenetic states) or extrinsic (for example, immune microenvironment) factors that may modulate cancer susceptibility independent of

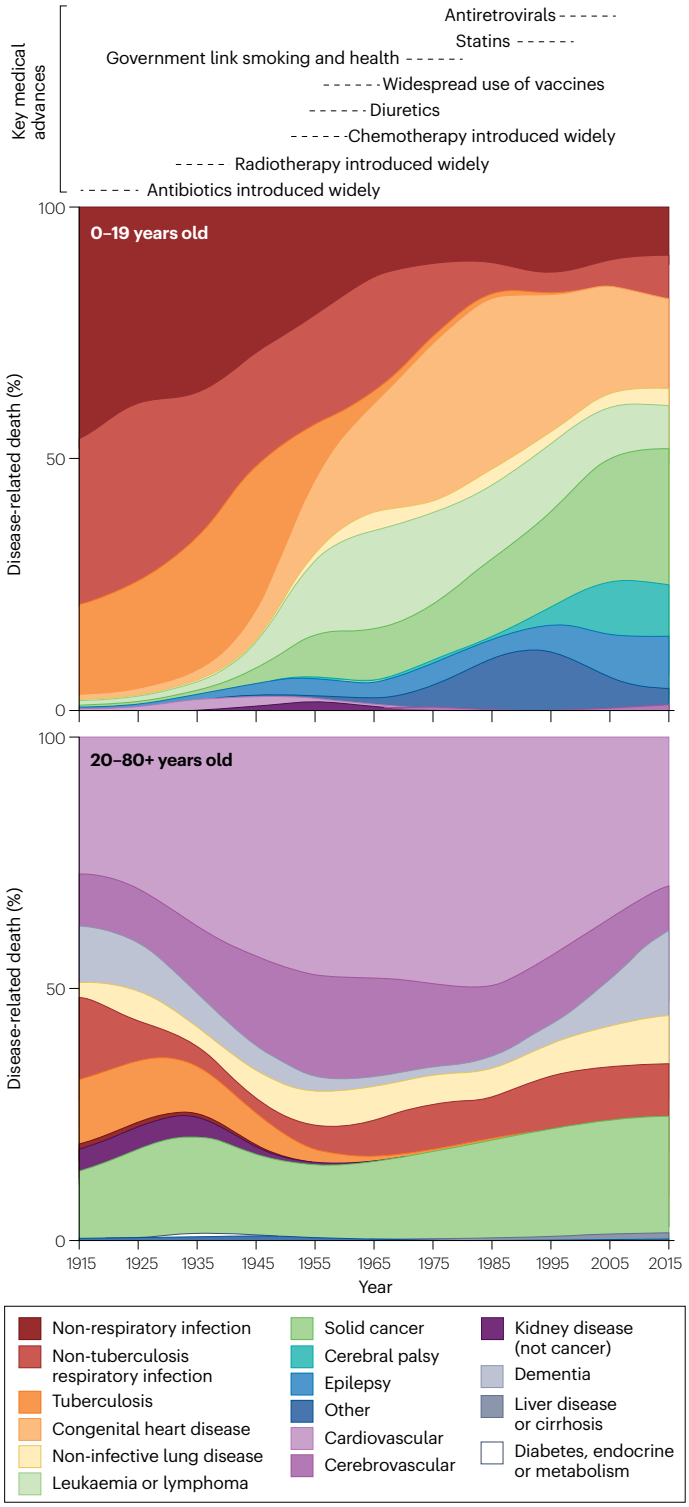

Fig. 1 | Major causes of disease-related death. The major causes of disease-related death recorded by the UK Office for National Statistics[2] between 1915 and 2015 in individuals 0–19 years of age (upper) or >20 years of age (lower). Hashed lines at top show the point at which the indicated major medical breakthroughs began to impact clinical practice.

cell division. Indeed, the mutation-centric nature of the theory assumes that extrinsic factors impact cancer risk merely through E-mutations rather than other processes such as changes in cell state (that is, metaplasia, discussed later in this Review) following tissue damage. This is particularly important in light of evidence that many carcinogens are not mutagenic[37], and mutational processes that are independent of cell division contribute substantially to somatic mutagenesis[43]. These shortcomings — shared by the somatic mutation theory — in part inspired the tissue organization field theory of cancer.

There are also technical concerns with the data used to support the bad luck theory. By necessity, many of the stem cell division metrics used by Tomasetti and Vogelstein[39] were not measured directly but were derived from comparisons of the total number of cells in each tissue with estimates of the number of resident stem cells. This approach does not account for age and non-malignant disease-related variations in the stem cell state that might impact cancer risk.

The ground state theory

We have proposed an alternative theory for cancer origins that focuses on the functional state of a cell (its 'ground state') rather than its classification as a stem, lineage-committed progenitor, or other cell type[40] (Fig. 3). This concept is important as it accommodates the notion of cell plasticity in which developmental, ageing and injury factors can alter the susceptibility of cells to transformation independent of cell division. This theory accords with the observation that many carcinogens are not mutagenic[37,44], and mutational processes that are independent of cell division contribute substantially to somatic mutagenesis[43]. Thus, the ground state theory builds on principles underpinning both the bad luck and tissue organization field theories, while emphasizing the convergence of extrinsic and intrinsic factors to generate the cell states that drive cancer. It is hoped that considering cancer origins in this manner will allow us to build on the success of epidemiological studies, and develop effective cancer prevention, early diagnosis and intervention strategies[20,21,45,46].

In contrast to the work of Tomasetti and colleagues, we formulated the ground state theory from observations made directly in genetically engineered mouse models[40]. Using in vivo lineage tracing we first recorded the stem cell capacity of specific populations of cells marked with prominin 1 (PROM1; also known as CD133, a well-recognized marker of certain normal and malignant stem cells[40,47]) in 14 major organs: lineage tracing is a gold standard in vivo test of stem cell function in which cells and their progeny are genetically labelled and tracked throughout life with a permanent fluorescent marker[48]. Cells were lineage traced in both neonatal and adult mice to understand how stem cell function might vary with age. In a parallel set of experiments, we measured the susceptibility of these same PROM1$^+$ cells to transformation in neonatal and adult mice by conditionally activating oncogenes (*Ctnnb1* (which encodes β-catenin), *Kras* or *Notch1*) and/or inactivating tumour suppressor genes (*Trp53, Pten* or cyclin-dependent kinase inhibitor 2A (*Cdkn2a*)).

In agreement with the bad luck theory, the level of stem and/or progenitor cell function of any given PROM1$^+$ cell correlated directly with its susceptibility to form cancer. This held true in the presence of multiple mutations regardless of the developmental stage at gene induction, strongly supporting the notion that stem cells dictate organ cancer risk. However, this risk varied markedly with age. On average, PROM1$^+$ neonatal cells were 7-fold more resistant to transformation than their adult counterparts. Cancer resistance in neonates was independent of stem cell proliferation, organ site and

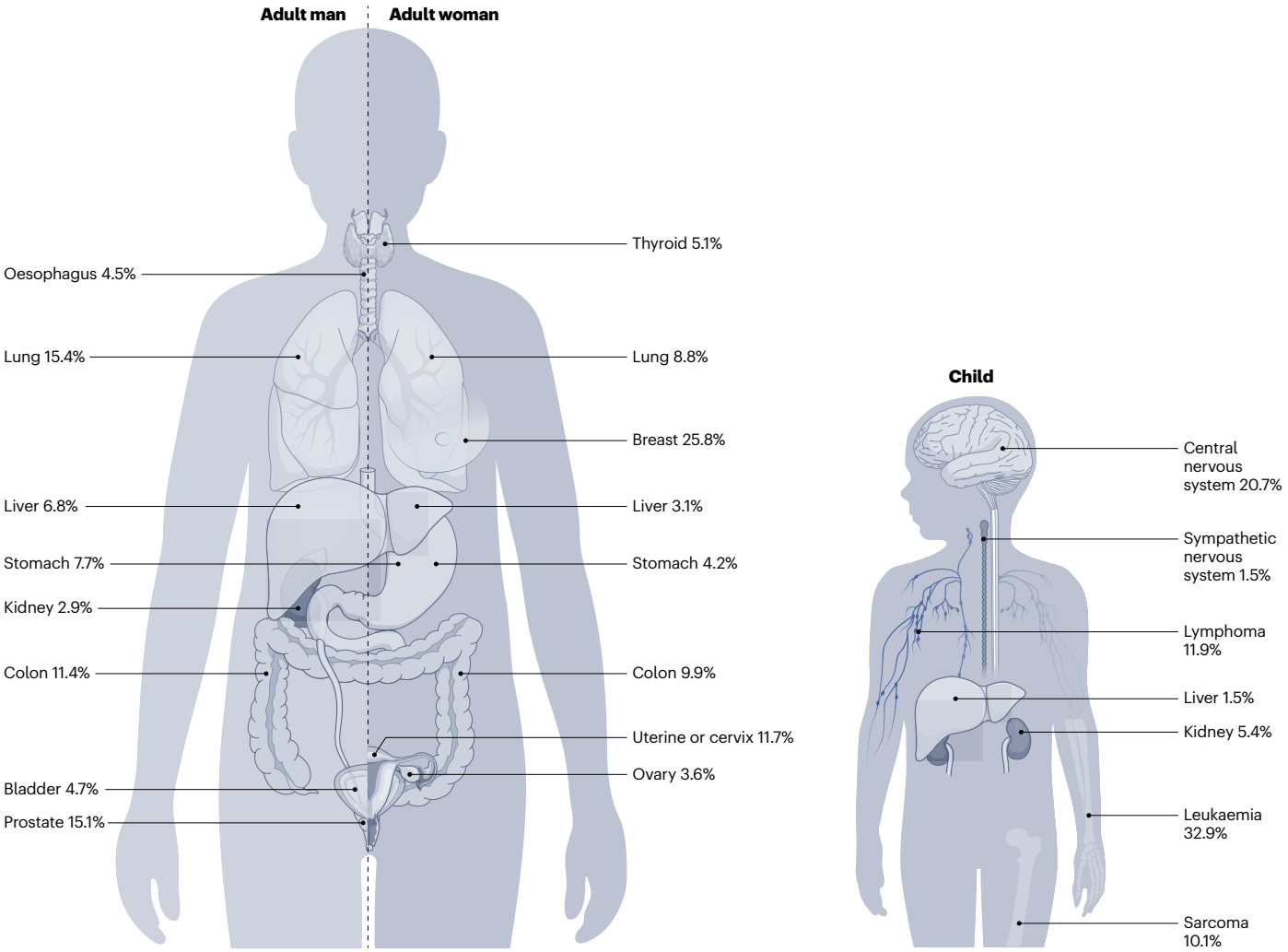

Fig. 2 | Organ sites of common human cancers. The major organ sites and types of adult (left) and childhood (right) cancer. Adult schematic reports male (left) and female (right) cancers. The percentage of the total cancer burden contributed by each cancer type is shown. Evidence of a cancer origin in stem and/or progenitor cells for some of the depicted cancer types can be found in refs. 40,47,57,59–68,75–86,88,90. Adult data obtained from the World Cancer Research Fund website, and childhood data from ref. 27.

lifelong persistence of mutations. It is tempting to speculate that multi-organ species have evolved cancer resistance mechanisms to protect tissues from transformation during the extreme mitotic and differentiation stresses of early development[49–51]. Thus, cancer risk is not merely an inevitable consequence of mutant stem cell proliferation but is also dictated by age-dependent, proliferation-independent variables in stem cells.

Comparative studies of embryonic, neonatal and adult haematopoietic stem cells (HSCs) support this notion, demonstrating the relative resistance of immature stem cells to transformation. For example, the FMS-like tyrosine kinase 3 (*FLT3*) internal tandem duplication mutation that is common in adult acute myeloid leukaemia (AML) but rare in childhood AML only induces transforming, self-renewal and myeloid commitment programmes once haematopoietic progenitors have transitioned from a fetal to an adult transcriptional state[52]. Similarly, differences in enhancer of zeste homologue 2 (EZH2)-dependent histone H3 lysine 27 (H3K27) trimethylation between leukaemias derived from the fetal liver and adult bone marrow restrict NOTCH1-driven autocrine insulin-like growth factor 1 (IGF1) signalling to fetal leukaemia stem cells, reducing their transplantability[53]. Beyond the blood, human fetal neural, liver and intestinal stem cells accumulate mutations at much higher rates than those of their adult counterparts and yet are far less likely to undergo transformation[54,55].

Importantly, the correlation between stem cell function and cancer risk does not vary solely with development. Rather, as discussed later in this Review, we and others have shown that quiescent adult stem cells carrying oncogenic mutations rarely transform, but readily generate cancer when activated to repair in the face of tissue injury[40,56]. Thus, in addition to developmental factors, cell extrinsic, environmental insults may impact cancer risk by changing the ground state of cells to a reparative, proliferative state.

But similar to the bad luck theory, there are caveats with observations underpinning the ground state theory. Species differences might limit the extrapolation of tumorigenesis from mice to humans, and mouse models that yield large numbers of cancers by simultaneously mutating millions of cells might not adequately recapitulate the transformation of human tissues that occurs through stochastic mutation of limited cell clones. Furthermore, the preselection of oncogenic mutations in mouse models might bias patterns of tumorigenesis. Nevertheless, the concepts and questions raised by the various theories of cancer origins provide a useful backdrop against which to debate the determinants of cancer risk and opportunities for cancer prevention.

Cell intrinsic factors

Cell identity

A fundamental element in understanding cancer origins is the identity of the cell(s) in each tissue that can undergo malignant transformation. As many leukaemias and solid tumours are hierarchically organized and sustained by a subpopulation of self-renewing cells, then stem cells — or cells that have acquired stem cell-like function, for example, in response to tissue damage — have been proposed as the origin of cancer in most tissues[40,47,57–65] (Fig. 2). Mouse models in which oncogenic mutations have been targeted to cells in different states of differentiation provide some of the most compelling evidence that cancers arise from stem cells[40,47,62,63,66–68]. Although some cancers can arise from committed progenitors or more differentiated cells, for example, certain leukaemias[69], it is generally agreed that cancers are propagated by populations of cells in a 'state of stemness'[70,71].

But epidemiological and functional studies demonstrate that cancer is not merely the consequence of randomly mutating stem cells. Tissue-specific patterns of mutations in sporadic cancers and organ-restricted patterns of tumorigenesis in inherited cancer syndromes demonstrate that cells are not equally susceptible to transformation and that different tissues are transformed by different oncogenic mutations[72,73].

Arguably, the clearest examples of how cell context determines the risk of developing certain cancers are provided by childhood malignancies (Fig. 4). Childhood cancers are typically not seen in adults because they arise from progenitor cells found only in the embryo, and some cannot be modelled in mice because they arise from human-specific progenitors. For example, unique progenitor populations within the human embryonic rhombic lip likely predispose humans, but not other species, to develop certain forms of the brain tumour medulloblastoma[74]. Studies in genetically modified mice have shown that anatomically, molecularly and clinically distinct subtypes of medulloblastoma and ependymoma — two relatively common forms of childhood brain tumour — arise from temporally and topographically restricted populations of neural stem and progenitor cells[66,67,75–77]. In these studies, the introduction of cancer subtype-specific mutations into all proliferating neural stem cells in the central nervous system transformed only distinct lineages. These lineages generated tumours that recapitulated the corresponding human cancer subtype. Notably, the epigenome and transcriptome of these susceptible neural stem cells are very similar to those of their daughter tumours, suggesting their epigenetic state is conducive and permissive to transformation by the

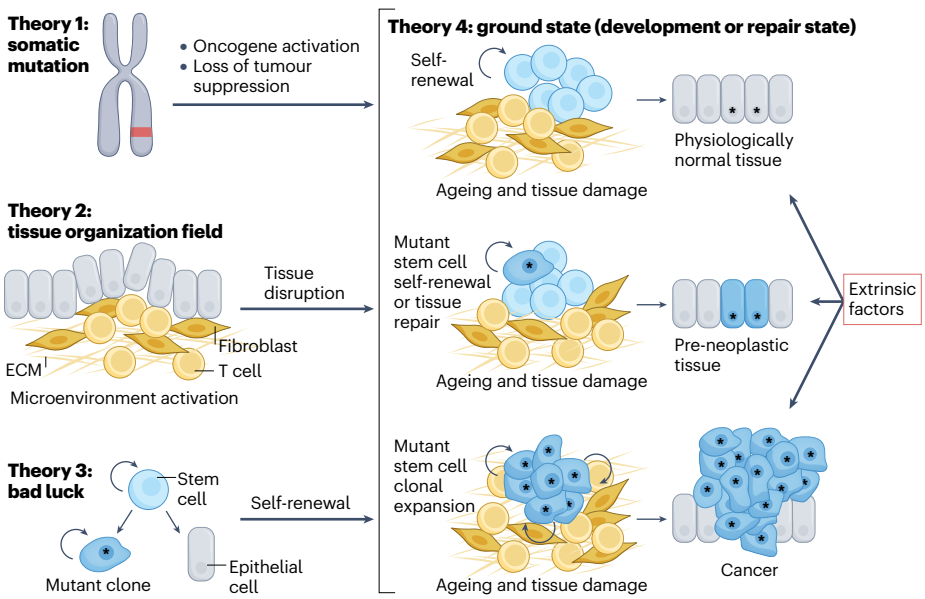

Fig. 3 | Principal theories of cancer origins. The somatic mutation theory (Theory 1) proposes that accumulating mutations in oncogenes and tumour suppressor genes transform cells, leading to unbridled proliferation and cancer. The tissue organization field theory (Theory 2) suggests that malignancies are driven at the tissue level by chronic abnormal interactions between the stroma and parenchyma. The stroma may include immune cells, extracellular matrix (ECM) and fibroblasts, among other elements. The bad luck theory (Theory 3) extends the somatic mutation theory, proposing that random mutations (marked with an asterisk) in self-renewing stem cells generate malignant, self-renewing, daughters that propagate cancer. The ground state theory (Theory 4) unites elements of the somatic mutation, tissue organization field and bad luck theories, emphasizing the important contribution of each to determining cancer risk. Exposure of ageing tissue stem cells to extrinsic cancer risk factors (for example, radiation, ultraviolet (UV) light, alcohol and tobacco) may result in tolerance of mutations by physiologically normal mutant clones with a ground state not conducive to transformation (top), metaplasia and pre-neoplastic lesions that may not progress (middle), and full malignant transformation (bottom).

Box 1

Shared elements among the different theories of cancer origins

The various theories of cancer origins emphasize distinct elements required for tissue transformation. The body of available evidence suggests that each of these elements contributes to cancer, although their relative importance may vary with cell context and cancer type.

Cell susceptibility states

Not every cell in the body makes cancer. The existence of cell susceptibility states is evidenced by the different cancers that arise in children and adults and the non-random distribution of cancers across the body. Although these patterns are dictated, in part, by differences in exposure to risk factors, they also arise because of the 'ground state' of a particular cell, in a particular place, at a particular time that renders it susceptible to cancer. This concept encompasses the notion of cell plasticity in which developmental, ageing or injury factors remodel the epigenome and transcriptome of cells establishing a transformable state.

DNA abnormalities

Changes in DNA sequence that activate the function of oncogenes (for example, point mutations, amplifications and translocations) or inactivate tumour suppressor genes (for example, nonsense mutations or deletions) have long been recognized as important for cell transformation. DNA abnormalities are important elements in all major theories of cancer origins. Historically, oncogenes and tumour suppressor genes were thought to predominantly impact fundamental aspects of the cancer phenotype such as cell proliferation and invasion. DNA abnormalities are now known to have much broader effects: remodelling the epigenome to generate a transforming, plastic cell state and cooperating with cell extrinsic factors, including tissue damage, to produce unique epigenomic states conducive to transformation.

Cell extrinsic factors

This element is central to the tissue field organization and ground state theories but emphasized less in the somatic mutation and bad luck theories. These include a plethora of factors ranging from physical mutagens to infective agents and tissue damage. A common theme includes the ability of these factors to induce metaplasia, producing a marked change in cell plasticity and increased risk of malignant transformation.

corresponding mutations[66,67,75–77]. Unaffected lineages throughout the rest of the nervous system appeared to tolerate these mutations, giving rise to apparently normal tissues[67] (Fig. 4). In medulloblastoma, this lineage restriction can be released by deleting DEAD box protein 3, X-chromosomal (*Ddx3x*), which encodes an ATP-dependent RNA helicase that regulates rhombomere patterning in the developing hindbrain, suggesting that broadening out the permissive epigenetic state to a larger number of stem cells increases cancer risk[78]. Subtypes of childhood high-grade glioma also appear to develop from stage and topographic-specific neural stem and progenitor cells[79–83].

Cell lineage-restricted susceptibility to cancer is not limited to childhood brain tumours but likely dictates the formation of most childhood leukaemias and solid tumours[84–90], as well as certain adult cancer types. For example, the *BRAF*^{V600E} mutation occurs in melanomas in which the tumour cells express a neural crest-like transcriptome, suggesting that this developmental state is competent for transformation[91,92]. Although neural crest and melanoblast stages are readily transformed by *BRAF*^{V600E} in zebrafish and human pluripotent stem cell models, melanocytes are relatively resistant[93]. The competency of neural crest cells and melanoblasts to transformation is dictated by stage-specific expression of the SRY-box 10 (SOX10) transcription factor and ATPase family AAA domain-containing protein 2 (ATAD2) chromatin factor that together promote the progenitor phenotype. Indeed, forced expression of ATAD2 in melanocytes renders them competent to transformation[93].

Together with evidence that neonatal stem cells are intrinsically resistant to cancer[40], these data underscore the identity of the cell of origin as a key determinant of cancer risk. This does not preclude the possibility that cancers result from random mutations of stem cells as suggested by the bad luck theory; however, as different stem cell populations are transformed by different mutations, even within the same tissue, and stem cells appear to show age-related differences in their susceptibility to transformation independent of proliferation, then additional forces must be at work to determine the susceptibility of specific cells to specific mutations.

The epigenome

What are these additional forces and characteristics that dictate cell susceptibility to transforming mutations? Among cell intrinsic factors, the epigenome is a major determinant of cancer risk that is constantly remodelled in developing and ageing tissues[94–96]. Indeed, promoter hypermethylation of developmental regulators characterizes transforming cells in vitro[97], and transient expression of reprogramming factors drives global changes in DNA methylation and tumorigenesis in transgenic mice[98]. Remarkably, pluripotent stem cells derived from these tumours generate non-neoplastic cells when transplanted in mice[98], demonstrating that they have escaped irreversible genetic transformation and that epigenetic regulation alone might drive cancer in certain contexts.

At least two broad types of epigenetic change impact cell state and cancer susceptibility. As alluded to above, the first involves the normal remodelling of chromatin and histone marks that occurs during development and ageing. Within the embryo, specific configurations of the epigenome in temporally and topographically restricted progenitor cells prepare them to generate the diverse daughters that populate each organ in each anatomical context. But these specific epigenetic states portend a cellular pliancy that also renders them uniquely susceptible to specific mutations[99,100]. Although we may have evolved mechanisms to suppress cancer during the intense mitotic and differentiation stress of early development, the requirement for

cellular plasticity in development may explain why cancer is rare, but not completely absent, during childhood.

Age-related remodelling of the epigenome may also contribute to the increased risk of cancer observed during ageing[101]. Changes in DNA methylation correlate strongly with chronological age in normal tissues, and there is some evidence that individuals who are 'epigenetically older' than their chronological age have an increased risk of cancer[102]. Epigenetic changes in ageing HSCs reinforce self-renewal and impede differentiation, establishing a genome landscape susceptible to transformation[103,104] (Fig. 5). Similarly, studies of cancer-free breast biopsies have revealed a strong correlation between chronological age and methylation changes[105]. Among 787 sites differentially methylated with age, many were in gene enhancer and transcription factor binding sites. Breast cancers displayed further deregulation of DNA methylation at these sites that were differentially methylated with age, rather than at alternative 'cancer-specific' sites.

A second group of changes to affect the epigenome and cancer risk includes mutations in histones and epigenetic regulators, as well as transcriptional silencing of tumour suppressors. Recurrent mutations in histones alter epigenomic patterning within gliomas, sarcomas and lymphomas, thereby disrupting fundamental DNA-templated processes including gene transcription and DNA damage repair[106]. Mutations in epigenetic modifiers may themselves create an epigenetic state permissive to transformation. Within the blood of ageing individuals, mutations in DNA methyltransferase 3A (*DNMT3A*), tet methylcytosine dioxygenase 2 (*TET2*) or *ASXL1*, which encodes a Polycomb group protein, lead to progressive expansions of haematopoietic clones (known as clonal haematopoiesis of indeterminate potential (CHIP)) and an increased risk of leukaemia[107–110]. Mutations of *DNMT3A* in HSCs or progenitor cells are an early premalignant event[111] that causes CpG hypomethylation at gene-regulatory elements, upregulating genes important in mediating stemness[106]. The subsequent accumulation of additional oncogenic mutations, facilitated by this shift in the epigenetic landscape, results in full transformation[111]. Intriguingly, CHIP may also increase the risk of cancers in solid tissues, although this needs to be validated and the mechanism understood[112]. With respect to the epigenetic silencing of tumour suppressor genes, this can include extensive regions of repressive chromatin that mimic large chromosomal deletions[113]. Thus, epigenetic remodelling that provides developing and ageing tissues with the plasticity needed to generate and maintain tissues may come with a price: the risk of priming these tissues for tumorigenesis.

DNA mutations: not the be-all and end-all?

Cancer has long been regarded as a disease of the genome[114]. The current body of massively parallel sequencing data derived from thousands

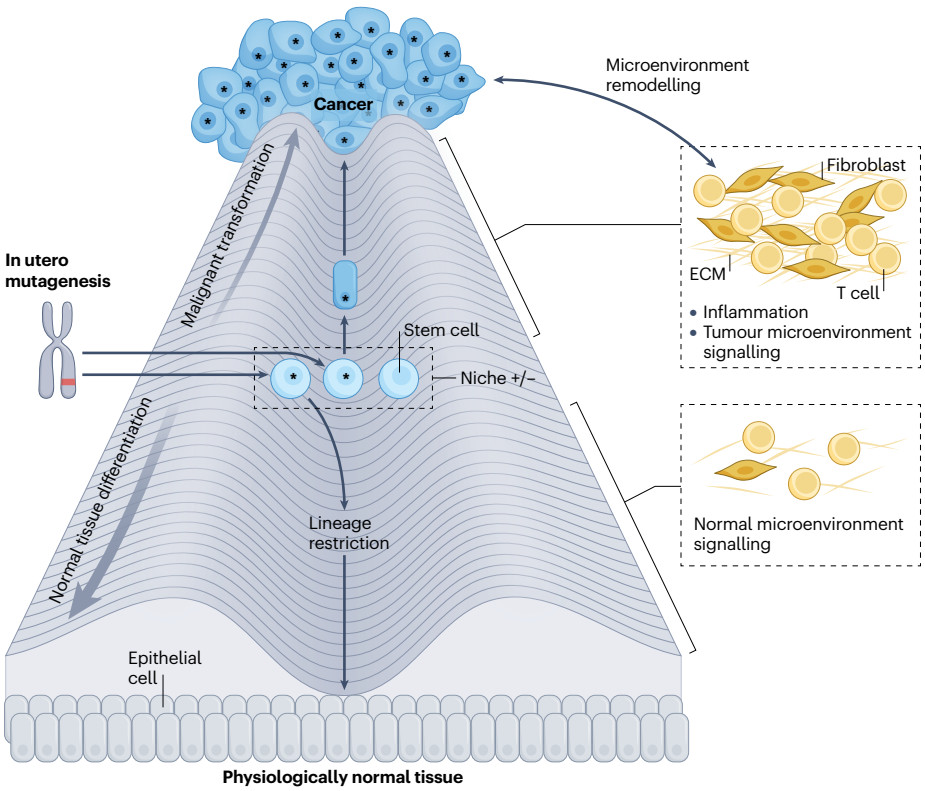

Fig. 4 | Origins of childhood cancer. Different types of tissue stem cells reside in stem cell niches that may have positive and negative (+/−) roles in transformation. A specific somatic mutation (asterisk), typically acquired by in utero mutagenesis, is tolerated by the first stem cell type (left) that undergoes lineage-restricted differentiation to form physiologically normal tissue. As this is the natural lineage trajectory, the process is represented as a downhill path (modified from Waddington's epigenetic landscape analogy)[211]. This process is supported by normal microenvironmental signalling. In contrast, the ground state of the second (middle) stem cell is susceptible to cancer driven by this specific mutation, initiating transformation. As neonatal stem cells are relatively resistant to cancer, this is represented as an uphill path. Signalling between the transforming cells and microenvironment remodels and contributes to this process and the cancer phenotype. ECM, extracellular matrix.

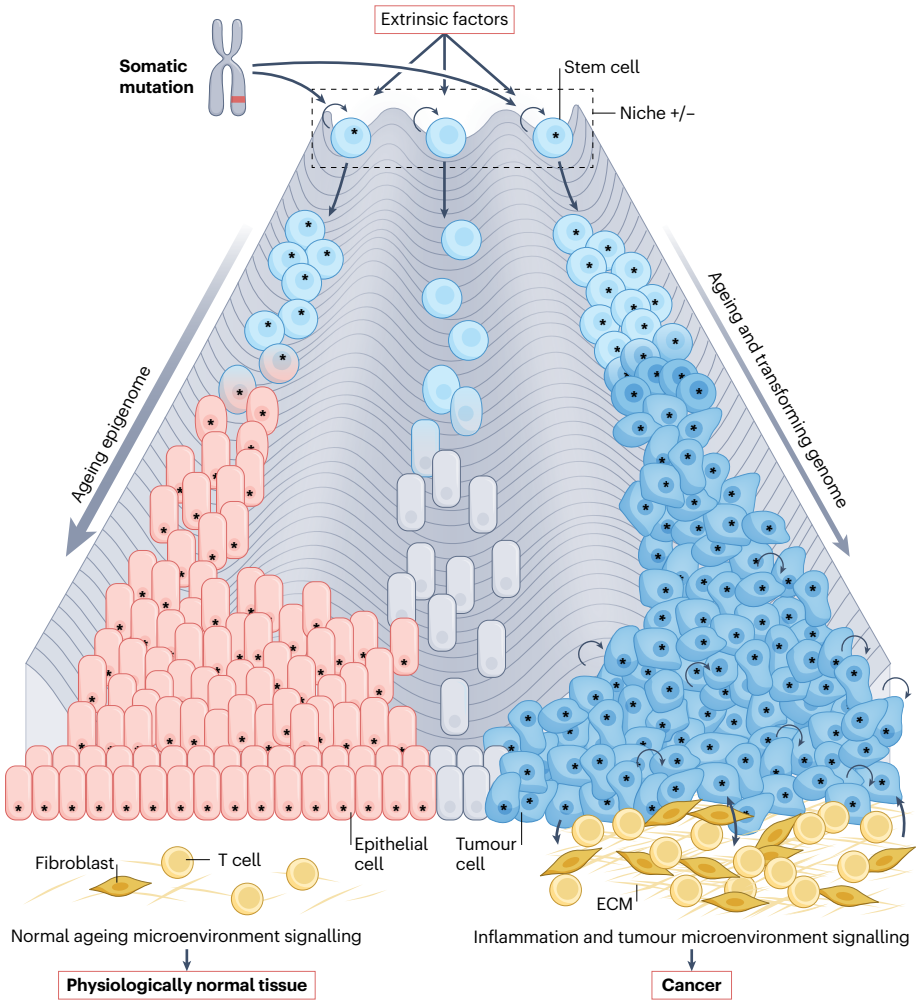

Fig. 5 | Origins of adult cancer. Different tissue stem cells, or cells that have acquired stemness characteristics through metaplasia, reside in stem cell niches that may have positive and negative (+/−) roles in transformation. A somatic mutation (asterisk), induced by extrinsic risk factors, is tolerated by the stem cell type on the left that subsequently undergoes lineage-restricted differentiation to form physiologically normal tissue. This natural lineage trajectory is represented as a downward slope (modified from Waddington's epigenetic landscape analogy)[211] and might be further favoured by the ageing genome that increases tolerance of mutations to enhance the proliferative and/or repair potential of ageing tissues. Non-mutant clones (stem cell lineage in the middle) are outcompeted by the mutant lineage (left), leading to aged tissues comprising mutant clones of physiologically normal tissue. Both lineages are supported by normal ageing microenvironmental signalling. The stem cell lineage on the right represents mutation of a susceptible stem cell, the accumulation of additional mutations and/or activation of a proliferative state that ultimately drives cancer formation. Signalling between the transforming cells and microenvironment remodels and contributes to this process and the cancer phenotype. ECM, extracellular matrix.

of human cancers has shown that tumours acquire an average of four or five 'driver' mutations and that this mutational burden increases with age. These data accord strikingly with predictions made decades ago from epidemiological studies that first inspired the somatic mutation theory of cancer and support the bad luck theory[29,32].

But the wealth of sequence data now available is unmasking a far more complex relationship between mutations and cancer risk. Historically, synonymous mutations — those that do not alter the protein sequence — have been thought of as mere passengers in cancer, whereas non-synonymous mutations have been regarded as 'drivers' of the disease. Indeed, large-scale CRISPR engineering studies in yeast suggest that synonymous and non-synonymous mutations similarly impact cell fitness, although this remains to be validated more broadly[115,116]. Furthermore, selection of synonymous mutations in oncogenes can impact RNA splicing and transcription in cancer[117,118]. Environmental influences are thought to determine which of these mutations are propagated by yeast. If similar environmental pressures operate to select oncogenic mutations in cancer, then this complicates the view that cancer is an inevitable consequence of mutating stem cells. Indeed, human stem cell-derived small intestine, colon and liver organoids acquire mutations at very similar rates despite marked differences in cancer incidence among their host tissues[119]. Furthermore, whereas juvenile tissues are resistant to cancer relative to those in adults, fetal neural, liver and intestinal stem cells accumulate mutations at much

greater rates than their adult counterparts[54,55] and have greater proliferative capacity[40]. Thus, factors other than mutations and stem cell proliferation likely determine whether or not a cell is susceptible to transformation.

Observations that large numbers of oncogenic mutations can be tolerated by physiologically normal tissues add weight to this argument. Although the skin of the eye lid rarely forms cancer, this apparently normal tissue harbours numerous driver-mutant clones[120], as do the ageing lung, oesophagus and colon[64,121–123] that are frequent sites of cancer. Although counterintuitive, the accumulation of such mutant clones is quite possibly a beneficial, even 'normal' feature of ageing epithelium (Fig. 5). The emergence of such clones in the oesophagus has been shown to have a surprising anti-tumorigenic role through the purging of early tumours by cell competition, thereby preserving tissue integrity[64]. Similarly, mutations in genes such as *PKD1*, which encodes polycystin 1, histone–lysine *N*-methyltransferase 2D (*KMT2D*) and AT-rich interactive domain-containing 1A (*ARID1A*) expand cell clones within the damaged human liver, and heterozygous deletion of these genes in mice is hepatoprotective against liver injury[124].

The choreography of cancer risk is therefore far more complex than previously appreciated: one in which the shifting landscape of developing, ageing and damaged stem cells determine their susceptibility to transforming mutations — a process compatible with the tissue organization field and ground state theories of cancer. This does not mean that the observations underpinning the bad luck theory are wrong, as the proliferative capacity of stem cells likely correlates closely with other facets of their identity. But understanding the precise characteristics of stem cells that render them susceptible to transformation, rather than attributing this merely to propagation of mutations through proliferation, is key if we are to develop effective cancer prevention strategies.

Box 2

Predicting cancer risk and more

Epidemiological research has identified chemicals and infective agents that cause cancer, leading to highly successful cancer prevention programmes. When combined with fundamental understanding of the biology of cancer origins, this knowledge can serve as the basis of systematic tools to stratify cancer risk. For example, a combination of genetic, lifestyle and imaging risk factors predicts 50% of women in the UK population with the highest risk of breast cancer, encompassing ~80% of all breast cancer cases in a 5-year period[212]. But a significant proportion of individuals at risk of cancer remain invisible to current prediction tools. The inclusion of additional biological risk factors might further improve predictive power. For example, detecting cancer-specific epigenetic profiles in accessible tissues, such as the uterine cervix or lymphocytes, or identifying such signatures in circulating cell free DNA is currently being investigated[96,213]. Alternatively, tracking expansions of premalignant clones might provide insights into the origin and early detection of malignancy. This work is most advanced in blood. Recent studies of >200,000 UK Biobank participants has enabled the mapping of inherited predisposition to clonal haematopoiesis — the clonal expansion of a blood stem cell and its progeny driven by somatic driver mutations[109,110]. This work has not only enabled the detection of clones years before the emergence of cancer but also the genes likely involved in this process, including those encoding regulators of DNA damage repair (poly(ADP-ribose) polymerase 1 (*PARP1*), ataxia telangiectasia mutated (*ATM*), checkpoint kinase 2 (*CHEK2*)) and haematopoietic stem cell (HSC) migration and homing (*CD164*), as well as known somatic drivers of myeloid oncogenesis (SET-binding protein 1 (*SETBP1*)). Remarkably, genetic predisposition to clonal haematopoiesis is not only associated with an increased risk of leukaemia but also of solid cancers and even non-malignant disorders such as atrial fibrillation[110]. Thus, rather than merely focusing on cancer risk, future epidemiological and biology-based strategies might consider disease risk more holistically, guiding patients through health pathways that seek to prevent and intervene in constellations of disease for which they are at particular risk.

Cell extrinsic factors

Extrinsic cancer risk factors — agents originating outside cells that can increase their risk of malignant transformation — have been recognized for more than 260 years[125]. Understanding how these agents increase cancer risk is important as this knowledge is central to cancer prevention (Box 2). Publication of the bad luck theory prompted vigorous debate because it raised concerns that it would deprioritize research of extrinsic factors and cancer prevention[126–131]. Subsequent studies published to redress the balance of debate suggested that intrinsic risk factors, including stem cell proliferation, contribute less than a third of lifetime risk to cancer development[132]. Protagonists on both sides of this argument have since published a consensus statement, agreeing that both cell intrinsic and cell extrinsic factors are important considerations in any comprehensive cancer prevention and treatment programme[133]. But transformational progress in cancer prevention will require not only an understanding of what intrinsic and extrinsic factors increase cancer risk but precisely how these interact in each tissue, developmental and ageing context to generate cancer.

Tumour microenvironment

The immediate surroundings of cells profoundly impact their behaviour. This is well illustrated by the niches that protect and regulate stem cells[134]. As stem cells, or cells that have acquired self-renewal properties, are the likely cell of origin of many cancers, these specialized niches are likely important regulators of cancer risk[135] (Figs. 4 and 5). Similar to normal neural stem cells, malignant stem cells in brain tumours occupy perivascular niches that regulate their function and are important for their survival[136,137]. Removal of these niches can inhibit tumour growth directly[136], whereas their retention protects brain cancer stem cells during treatment, allowing them to propagate disease relapse following radiotherapy[138]. Given the widespread distribution of these niches throughout tumours, it is likely that cancers can create these self-sustaining microenvironments. Evidence of this can be seen in mouse models of squamous cell carcinoma in which an interleukin-33 (IL-33)–transforming growth factor-β (TGFβ) feedback loop between stem-like tumour initiating cells (TICs) and macrophages creates a niche crucial for tumour progression[139].

Although corruptible, niches might also suppress stem cell transformation. The balance of collagens, proteoglycans and glycoproteins in the extracellular matrices (ECMs) that line stem cell niches constrains their transformation[140–143]. Indeed, communication between tumour stroma and malignant cells can remodel the ECM, dictating whether

Glossary

Apolipoprotein B mRNA-editing enzyme catalytic polypeptide
(APOBEC). An enzyme that edits mRNA species by deaminating cytosine to uracil.

Barrett oesophagus
A precursor condition for oesophageal cancer in which there is an abnormal (metaplastic) change in the mucosal cells lining the lower portion of the oesophagus, from stratified squamous epithelium to simple columnar epithelium.

Blastocysts
Clusters of dividing cells made by a fertilized egg, comprising the early stage of an embryo.

Developmental regulators
Genes that play an important role in the control of normal tissue development.

Dysplasia
The presence of abnormal cells within a tissue that may represent the precursor of malignant change.

Ependymoma
The third most common brain tumour of children arising from radial glia throughout the neural axis.

Internal tandem duplication
Duplication of sections of DNA adjacent to the original sequence.

Medulloblastoma
The most common malignant brain tumour to affect children, arising in the hindbrain from progenitor cells of the upper or lower rhombic lips.

Melanoblast
A neural crest-derived precursor cell of melanocytes, the cells that make pigment in the skin.

Metaplasia
The emergence of new cell types or disproportionate numbers of normal cell types.

Reprogramming factors
Transcription factors including OCT3 and OCT4, SOX2, MYC and KLF4 that can convert a differentiated somatic cell state into a pluripotent embryonic-like state.

Rhombomere
A transiently divided segment of the developing neural tube within the hindbrain.

Telomerase reverse transcriptase
(TERT). Part of a distinct subgroup of RNA-dependent polymerases that lengthen telomeres (the ends of DNA strands).

cancers progress[144,145] (Figs. 4 and 5). In mice with breast cancer, malignant mammary epithelial cells and breast fibroblasts interact through the formation of a PTEN–ETS2 signalling axis that suppresses breast cancer through the extensive remodelling of the ECM. Loss of *PTEN* from these stromal fibroblasts accelerates tumour initiation and progression in a manner dependent on *ETS2* expression within tumour cells[144,145]. The embryonic ECM has also been suggested to suppress cancer[146]. Thus, the relative resistance of embryonic and neonatal stem cells to cancer likely involves a complex interaction between cell extrinsic and intrinsic properties[40].

Immune cells that survey and remove sick and infected cells from tissues are also important modulators of cancer risk[147]. This notion is supported by the increased incidence of cancer in patients who are immunosuppressed[148]; the infiltration of aggressive cancers with specific immune cell subsets[149]; the more efficient development of tumours in mice with deficient $CD8^+$ cytotoxic, $CD4^+$ T helper 1 (T_H1) and/or natural killer cells[150,151]; and the success of therapies that enable cancer cell killing by the immune system[13,14]. Immune cells are thought to survey tissues constantly, recognizing and removing 'non-self' mutant cancer cells[147]. Although cancers can escape this surveillance by evading immune recognition[152,153] and/or developing an immune-tolerant microenvironment[154,155], a question of relevance to cancer origins is whether stem cells are peculiarly susceptible, or resistant, to this surveillance. Elegant systems that measure antigen-dependent interactions between T cells and tissue stem cells are beginning to provide answers to this question[156]. One such study has shown that whereas intestinal, ovarian and mammary adult stem cells are eliminated by activated T cells, quiescent stem cells in other tissues resist T cell killing[157]. This appears to be an intrinsic property of quiescent stem cells that downregulate antigen presenting machinery — a property that is reversed when stem cells re-enter the cell cycle.

Communication between transforming cells and their microenvironment is therefore likely to modulate the capacity of epigenetically primed and mutated stem cells to generate cancer. This includes complex relationships with niche environments that cancers may corrupt and/or create, as well as interactions with the host immune system.

Infections and the microbiome

Microorganisms that invade tissues have long been recognized as important extrinsic determinants of cancer risk[158–161]. The bacterium *Helicobacter pylori* is the most common infection-related cause of cancer[161]; the next four most frequent are viruses[160], including human papilloma virus (HPV), hepatitis B virus (HBV), hepatitis C virus and Epstein–Barr Virus. Similar to other cancer risk factors, these infections can create an epigenome permissive to transformation, create a genome instability that leads to oncogenic mutations or remodel the microenvironment to a state conducive to cancer formation.

HBV promotes hepatocellular carcinogenesis by inducing host genome instability and epigenetic remodelling following viral integration; activating cancer-related signalling pathways; and remodelling the immune microenvironment by inducing chronic inflammation[162]. Epstein–Barr Virus, the first isolated human tumour virus[163], remodels the host cell genome, methylating and downregulating tumour suppressor genes[164]. HPV encodes various proteins, notably E6 and E7, that degrade, or interfere with the function of, tumour suppressor proteins[165].

Next-generation sequencing of human cancers has provided further understanding of the mechanisms underpinning viral-mediated transformation. Telomerase reverse transcriptase (TERT) — an established driver of carcinogenesis — is frequently upregulated by integration of HBV at the gene's promoter site[160,166], whereas HPV-integrated cancers are characterized by apolipoprotein B mRNA-editing enzyme catalytic polypeptide (APOBEC)-associated mutations[160]. As APOBEC changes viral genome sequences as a cellular defence against viruses[167], its activation following viral integration might introduce cancer-causing mutations within the host tissue genome.

In addition to bacteria and viruses that cause infectious disease, there is increasing evidence that commensal microorganisms — collectively termed the microbiota — influence cancer risk[168]. This has been demonstrated most convincingly with the intestinal microflora. For example, *Fusobacterium nucleatum* promotes colorectal cancer by direct binding of cancer cells through the bacterial adhesin FadA, which in turn leads to upregulation of β-catenin signalling and promotion of a pro-inflammatory microenvironment[169,170].

When considering cancer origins, it is important to determine whether all cells in a tissue, or just rare subpopulations such as stem cells, are susceptible to commensal and/or infection-mediated transformation. Evidence from HPV-associated cancer suggests that viral-mediated transformation might be cell selective. Although HPV can infect the entire genital mucosa, malignant transformation occurs most commonly at the junction of the columnar endocervix and the squamous ectocervix[171]. This region comprises two types of specialized epithelial cells with stem-like properties, which regenerate the endocervix and ectocervix. Furthermore, HPV transformation is far less common at the transformation zones of the vulva, vagina and anus that comprise differentiated and multilayered epithelia[172]. Thus, the self-renewal capacity and residence within an immune-privileged niche may contribute to the susceptibility of these cells to transformation[173].

Mutagens

Massive parallel sequencing has not only identified which genes are mutated in cancer and how often but also enabled the segregation of these into >40 specific signatures likely caused by distinct mutagenic processes[174–176]. These signatures include signatures of single-base substitutions associated with exposure to chemotherapies, ultraviolet (UV) light, occupational carcinogens or endogenous enzymatic mutagenesis, for example, via the DNA cytidine deaminase APOBEC3 family. These signatures may be used to predict potential causative carcinogens in specific cancer types.

Evidence suggests that two of these signatures, referred to as 'clock-like', accumulate steadily throughout life from the fertilized egg to the cancer cell[176]. The inevitability of such mutations accords with the bad luck theory of cancer origins. Indeed, some of these mutations predominate in cancers derived from highly proliferative epithelia, for example, the stomach and colorectum[176]. But 'clock-like' mutations are not inevitably propagated by lifelong stem cell proliferation. Their incidence varies markedly among cancer types in a manner that does not always correlate with lifelong proliferative capacity. Indeed, two different embryonal tumours of the developing nervous system are among those with the highest (neuroblastoma) and lowest (medulloblastoma) incidence of these mutations[176]. Thus, at least in some contexts, alternative, proliferation-independent mechanisms are likely to underpin the generation of these mutations.

Notably, the impact of mutagens on cancer risk can also be modified by the ground state of the cell. Alcohol is a known carcinogen that increases the risk of several human cancer types[177–179]. The alcohol-derived metabolite acetaldehyde causes DNA double-stranded breaks and chromosome rearrangements in HSCs in mice[180]. Acetaldehyde-damaged HSCs are repaired by the Fanconi anaemia cross-link and non-homologous end-joining DNA repair pathways and removed by the p53 response pathway. Deletion of *Trp53* rescues HSC defects and increases the pool of mutant HSCs. Thus, intrinsic properties of stem cells including genome stability, DNA repair and cell death pathways might modify the ultimate impact of extrinsic factors on cancer risk.

The convergence of cancer risk factors

Given the close similarities between cancer and the physiological states that have evolved to maintain and repair ageing tissues, it is not surprising that one in two of us eventually develop some form of malignancy[181]. Whether a particular cell, in a particular place, at a particular time departs from its normal lineage to produce malignant tissue is likely to be determined by the convergence of context-specific cell intrinsic and extrinsic risk factors. This process is enabled by permissive epigenetic, plastic cell states that have evolved to support normal development and ageing. This susceptibility is likely characterized by existing or acquired self-renewal — the process by which stem cells divide to make more stem cells, ensuring that their population is maintained or expanded for long-term clonal growth[70,71,182]. Remarkably diverse but predictable patterns of DNA mutations, acquired through enzymatic, infective, chemical or physical mutagens, hardwire and corrupt self-renewal capacity. Remodelling of communication between cells evolving towards a malignant state and their immediate microenvironment progresses the tumour.

Although it is helpful to consider cancer determinants as either cell intrinsic or cell extrinsic, exploiting this knowledge to diagnose and intervene early in the disease process will require understanding of how these factors interact to determine cancer risk.

The interface of intrinsic and extrinsic risk factors

Berenblum and Shubik[183] first suggested 75 years ago that cancers are formed through a carcinogen-driven initiation phase that is followed by an irritant-driven promotion phase when latent tumour cells are provoked to proliferate. Research conducted over the following decades has highlighted the importance of tissue damage and inflammation in cancer risk[184]. This encompasses overt injury associated with chemical or infective agents as well as the subtle wear and tear associated with ageing[185–189].

Metaplasia is a key feature of the tissue damage response[190]. Although metaplasia can take different forms in different tissues, it is characterized by a marked change in cell plasticity. Lineage-restricted progenitors in hair follicles that do not normally produce skin epithelial cells can repair epithelial lineages following extensive skin damage[191]; and differentiated secretory cells of the lung de-differentiate to replace damaged airway basal stem cells[192]. Metaplasia can even involve the emergence of new cell types not seen in the normal tissue, as observed in Barrett oesophagus[190]. Similar to cell plasticity associated with development and ageing, metaplasia is important for repairing damaged tissues through the expansion of cell populations with stem cell-like properties; but it carries the risk of an increased likelihood of transformation[190].

Studies of genetically engineered mice support this hypothesis. Cooperation between oncogenic mutations in *Kras* and tissue injury remodel the pancreatic epigenome, producing thousands of chromatin accessibility changes not caused by mutant *Kras* or injury alone[193]. Interestingly, this process also involves IL-33 that is a key element in the generation of TIC niches in squamous cell carcinoma discussed above[139]. Thus, oncogenic mutations and tissue injury can together remodel chromatin to promote neoplasia-specific transcriptional programmes. Similarly, adult liver stem cells carrying oncogenic mutations are quiescent and resistant to cancer, but are activated following tissue damage, increasing cancer risk 40-fold (ref. 40); and air pollutants promote the proliferation of latent clones of *Kras* or epithelial growth factor receptor (*Egfr*)-mutant lung epithelia to generate adenocarcinomas[56].

Changes in the microenvironment may also contribute to this perfect storm of cancer risk factors. For example, changes in the physical stiffness of tissues that may result from cycles of damage and repair activate Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) target genes to increase cell susceptibility to transformation[194]. In the lung, tissue damage appears to increase cancer risk only in animals with a competent immune system[56].

This may well be mediated by macrophage-derived secretion of IL-1β (refs. 56,195). Thus, whereas the immune system plays a key role in cancer surveillance by removing mutant cells with malignant potential[147], it might also promote cancer when responding to tissue damage and inflammation.

In many tissues, damage activation of adult stem cells is associated with a partial reversion to an ancestral, immature state[40,56,196–199]. This seems logical as embryonic-like stem cells might regenerate tissues optimally. But the reparative capacity and cancer-suppressing properties of activated adult stem cells is limited relative to their juvenile counterparts[40,200,201]. Thus, comparisons of embryonic and damage-activated adult stem cell transcriptomes might unmask novel cancer-suppressing processes.

This concept is not unique to cancer. Although neonatal mammals can readily regenerate heart muscle, this capacity is lost in adults[202]. Similar to the cancer suppression programmes that may operate in neonates and are lost in adults, injured adult heart reactivates a fetal-like programme that produces injury-induced hypertrophy but not myocardial regeneration[202]. Full reactivation of cardiac regeneration in the injured adult heart could transform the treatment of myocardial infarction. Thus, interdisciplinary collaborations that seek to reactivate embryonic regenerative programmes safely could transform medicine, enabling restoration of damaged adult tissues to a fully functioning, disease-free state.

Metastasis

Most cancer-related deaths are not caused by the primary tumour but are the consequence of metastatic spread[203,204]. Thus, if one considers cancer risk in terms of its threat to human health, then the risk lies not merely in the transformation of tissues but in its propensity to metastasize. Understanding and preventing this process would markedly reduce the risk posed by cancer.

Similar to the cell susceptibility states required for tumour initiation, circulating tumour cells capable of seeding metastases are thought to be stem-like[203,205,206]. This plasticity has focused largely on studies of epithelial-to-mesenchymal transition (EMT) and mesenchymal-to-epithelial transition (MET) that occur when tumour cells leave the primary cancer, enter the bloodstream, travel to distant sites and re-establish a tumour mass[207]. Although EMT is also a feature of gastrulation in the embryo[208], in the context of cancer this process is thought to be wholly abnormal and a pathological consequence of transformation.

However, increasing evidence suggests that the metastatic cascade can be divorced from upstream tumorigeneisis[209,210]. Initial studies demonstrated that untransformed mouse mammary epithelial cells injected into mice seed morphologically normal microcolonies in the lung[209]. Activation of inducible oncogenes in these cells then results in the formation of metastases. Subsequently, we have identified the sodium leak channel non-selective protein (NALCN) as a key regulator of cancer metastasis and non-malignant cell dissemination[210]. Deletion of *Nalcn* from malignant or normal epithelia in mice equally mobilized epithelial stem cells into the blood: these cells trafficked to distant organs to make metastatic cancer or apparently normal tissues, respectively. We propose that this process occurs throughout life to supply reparative stem cells to distant damaged organs. Therefore, metastasis might be regarded as an otherwise normal process that is hijacked, rather than 'created', by cancer. If this mechanism is validated in human cancer, then these findings present an even more complex picture of cancer origins in which tissue damage, stem cell activation and mutations conspire to promote tumorigenesis and metastasis.

Conclusions

Preventing cancer, or treating it before it becomes incurable, will require a full understanding of the intrinsic and extrinsic factors that increase the risk and spread of malignancy. This understanding could transform cancer from the uniformly feared disease it is today into one that is manageable and not life-limiting.

A unifying element in the pathophysiology of cancer may prove to be cell plasticity and stem cell self-renewal machinery that enable cancers to propagate malignant clones unchecked, providing fertile ground for discovering new early cancer diagnostic and intervention strategies. Emerging evidence that ageing epithelia comprise ever expanding numbers of mutant stem cells, perhaps to retain tissue fitness, indicates that our view of oncogenic mutations needs to be far more sophisticated than that currently held. It must recognize and understand how ageing organs 'walk a tightrope', constantly balancing the need to maintain declining tissues by adjusting their genomes towards a pro-repair state, while avoiding the risk of overstepping into transformation. Evidence that juvenile stem cells are intrinsically resistant to cancer relative to their adult counterparts might provide a navigable route through this complexity, as direct comparison of these states could unmask novel cancer suppression mechanisms that have evolved to protect immature developing tissues. If these can be safely resurrected in ageing stem cells, then the impact on cancer prevention could be profound and highly effective.

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Author contributions

All authors researched data for the article and contributed substantially to discussion of the content. R.J.G. and A.J. wrote the article. All authors reviewed and/or edited the manuscript before submission.

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