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Review

Impact of risk factors on early cancer evolution

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https://doi.org/10.1016/j.cell.2023.03.013

SUMMARY

Recent identification of oncogenic cells within healthy tissues and the prevalence of indolent cancers found incidentally at autopsies reveal a greater complexity in tumor initiation than previously appreciated. The human body contains roughly 40 trillion cells of 200 different types that are organized within a complex three-dimensional matrix, necessitating exquisite mechanisms to restrain aberrant outgrowth of malignant cells that have the capacity to kill the host. Understanding how this defense is overcome to trigger tumorigenesis and why cancer is so extraordinarily rare at the cellular level is vital to future prevention therapies. In this review, we discuss how early initiated cells are protected from further tumorigenesis and the non-mutagenic pathways by which cancer risk factors promote tumor growth. By nature, the absence of permanent genomic alterations potentially renders these tumor-promoting mechanisms clinically targetable. Finally, we consider existing strategies for early cancer interception with perspectives on the next steps for molecular cancer prevention.

INTRODUCTION

How and why tumors arise has occupied the medical profession and biologists for centuries. A patient with breast cancer is described in a 3,500-year-old papyrus,[1] and across the centuries, hypotheses on what causes cancer have ranged from unbalanced humors,[2] "diet, lifestyle, emotions, environment, and age,"[3] to contagion.[4,5] In 1914, Theodore Boveri suggested that cancer might form from a single cell due to an aberrant chromosome content,[6] and in 1928, Karl H. Bauer published his hypothesis that mutations were the cause of cancer.[7] It is now well accepted that cancer is a disease caused by alterations to DNA that grant a selective advantage to a cell, resulting in malignant growth. A great amount of research has been directed into the nature and causes of the genomic landscapes within malignancies; now the modulators of the selective advantages conferred by such genetic aberrations warrant similar intensive focus.

In this review, we borrow the terms "initiator" and "promoter" from Berenblum and Shubik[8] and, more recently, Balmain and colleagues.[9] We define an initiated cell as one containing a heritable alteration that could permit a selective advantage over its neighbors. This mutated cell might remain indolent or be triggered to expand into a pre-invasive lesion following tissue homeostasis perturbations. The pre-invasive lesions can remain occult during the host's lifespan,[10–13] or be subject to a series of selection pressures to eventually form an invasive lesion acquiring the hallmarks of cancer.[14] Each stage of tumorigenesis—from initiation, via expansion of pre-malignant clones, to acquisition of invasive properties—has the potential to be affected by cancer risk factors through cell intrinsic and extrinsic mechanisms (Glossary, Figure 1).[15] Here, we will delineate the early steps of solid cancers, focusing on the mechanisms by which risk factors can alter or "promote" the constraints on tumor initiation via non-mutagenic pathways. Such pathways, by virtue of not inducing permanent genomic scars, are potentially reversible, which has implications for clinical cancer prevention strategies.

RISK FACTORS AND TUMOR INITIATION

Categories of risk factors

Early efforts to identify environmental exposures associated with cancer incidence have been described since the 18th century. In 1775, Percivall Pott reported the association of chimney soot and scrotal cancer,[16] providing some of the first evidence linking environmental exposure to cancer initiation, later supported by the functional studies of Yamagiwa and Ichikawa.[17] It is now estimated that 44% of cancers are attributable to potentially modifiable behavioral, environmental, and occupational risk factors,[18] with the rising incidence of early-onset cancers potentially linked to such exposures.[19] In this review, we broadly define risk factors as those associated with an increased incidence of a given cancer and build upon the definitions of Hannun and colleagues[20] to categorize these cancer risk factors as (1) exogenous risk factors that are largely modifiable and refer to the external environment of the host (infection, lifestyle, and exposures) or endogenous risk factors that may be modifiable and relate to the individual characteristics of the host; including (2) initiating cell extrinsic factors (e.g., immune responses, oxidative

Glossary.

Cancer risk factor: a determinant that is associated with increased incidence of cancer. These can be further classified as exogenous risk factors (e.g., cigarette smoking or infections, often modifiable by lifestyle) and endogenous risk factors. The latter can be further divided into those that are cell extrinsic (e.g., immune, hormonal, microbiota) and those that are cell intrinsic (e.g., inherent DNA replication errors in cell turnover, DNA repair ability). Endogenous risk factors are dependent on the characteristics of an individual and include germline susceptibility.

Cell fitness: the ability of a cell to thrive in a defined environment and can be altered by a range of intrinsic and extrinsic parameters.

Cell of origin: the cell acquiring a tumor initiating heritable alteration(s) leading to the eventual formation of an invasive cancer. Tumor initiating cells are distinct from cancer stem cells, which are defined as cells developed throughout tumor progression that fuel malignant growth.

Indolent lesions: pre-invasive or invasive lesions that do not progress in a patient's lifetime to interfere with quality of life or life expectancy.

Oncogenic competence: the ability of a given cell to form a tumor upon activation of a driver oncogene or inactivation of a tumor suppressor known to cause cancer, combined with the likelihood of a cell acquiring such alteration(s) within its genome. This property is cell intrinsic, yet tumor formation is influenced by cell extrinsic factors (e.g., cell position within a tissue structure may alter the outcome of tumor formation).

Oncogenic switch: The transition from a localized, pre-invasive neoplasia to invasive carcinoma. Hallmarks of the switch include acquisition of copy number alterations, chromosomal instability, tolerance of genome instability, immune escape, invasion into surrounding tissue, and microenvironmental remodeling. See Box 2.

Tumor initiation: The acquisition of a heritable alteration within a cell in a genomic locus known to cause the formation of cancer.

Tumor promotion: mechanism by which some cancer risk factors can act on healthy cells or initiated cells to promote tumor progression at any stage of carcinogenesis.

stress, microbiome, metabolism, endocrine regulation), and (3) initiating cell intrinsic factors (e.g., DNA damage response, fidelity in DNA replication, cell cycle checkpoint regulation, oxidative stress response, chromatin architecture, transcriptional and translational networks), where cell extrinsic factors are likely more readily modifiable. The so-called "bad luck" of tumor initiation that arises due to random errors in DNA replication upon cell division is encompassed in the cell intrinsic category[21] (see Box 1); yet, each risk factor category is not distinct, and the likelihood of cancer formation encompasses the integration of all three categories; for example, a lifetime of tobacco smoking (1) will be influenced by individual susceptibility dependent on (2) and (3).[22,23] In this review, we will focus on the molecular mechanisms by which exogenous cancer risk factors (defined in Table 1) function to allow for tumorigenesis or tumor progression.

Mechanisms of action of cancer risk factors

Much focus has been dedicated to uncover the mutagenic properties of risk factors detectable by distinctive mutation patterns within the tumor genome, known as mutational signatures (reviewed in Koh et al.[52]). Mutational signatures associated with UV radiation are detected within melanoma[53]; similarly, *Helicobacter pylori*-derived signatures within gastric cancers[54,55] and tobacco-associated signatures in lung, larynx, pharynx, oral, esophageal, and liver cancers[56] where the specific $KRAS^{G12C}$ driver mutation is associated with a smoking signature in lung adenocarcinoma.[57] This suggests that some risk factors generate oncogenic driver alterations necessary for tumor initiation (Figure 1); however, the precise origins of some mutagenic signatures remains unclear.[52,58] Advances in DNA profiling technologies have allowed the identification of rare events in expanding clonal populations *in vitro*,[59] microdissection of clonal units,[60] or in whole tissue samples using error-corrected sequencing.[61] This has revealed a patchwork of mutations within histologically normal tissues (reviewed in Kakiuchi and Ogawa[62] and Marongiu and DeGregori[63]). Mutational signature analysis has also been applied to histologically normal tissue and unveiled mutational signatures associated with tobacco exposure, UV light, aging, and inflammation.[59,60,64–66] This suggests that oncogenic driver mutations arise throughout one's life and can be elevated by exposure to exogenous risk factors. That the formation of cancer is exceedingly rare compared to the incidence of oncogenic driver mutations within otherwise healthy tissues, as well as the ubiquity of indolent lesions that do not progress to invasive disease (see Glossary, Box 2), highlights that mammals must have evolved multiple mechanisms to restrain mutant cells from becoming a cancer.

Riva et al.[76] discovered that 17 of 20 carcinogens given to mice failed to significantly increase the resulting tumor mutation burden. Furthermore, 24 of 79 environmental agents given to human induced pluripotent stem cells (iPSCs)[58] did not generate a readily classifiable mutational signature. These results provide support for the notion that endogenous processes contribute to the acquisition of key cancer driver mutations and that carcinogens may act in non-mutagenic ways to promote cancer. Indeed, our recent analysis from TRACERx has demonstrated that 8% of patients with a significant history of tobacco exposure with adenocarcinoma of the lung harbor tumors with no detectable tobacco carcinogenic mutational signature.[28] Genetic profiling of tumor mutations and mutational signatures has revealed that not all oncogenic driver mutations are a result of environmental exposures. Many of the observed mutational signatures have been correlated with endogenous sources of DNA damage, such as spontaneous deamination, aging, APOBEC-mediated editing, DNA repair deficiencies, and reactive oxygen species. *In silico* analysis has revealed that many key oncogenic driver mutations found in cancers (e.g., $BRAF^{V600E}$, $KRAS^{G12D}$, $TP53^{R175H}$, $NRAS^{Q61K}$) correspond to an aging signature, rather than with signatures associated with environmental exposure, raising questions as to the mechanisms of mutagenic environmental exposures in cancer development.[77] A similar conclusion was reached in the Mutographs project[78] that profiled over 500 whole genomes from esophageal tumors from eight different countries with varying esophageal cancer incidence rates. It was found that the mutational profiles were strikingly similar. This lack of any clear mutational differences between tumors from high-risk and low-risk areas suggests that risk factors that leave no measurable genomic imprint on tumor DNA may

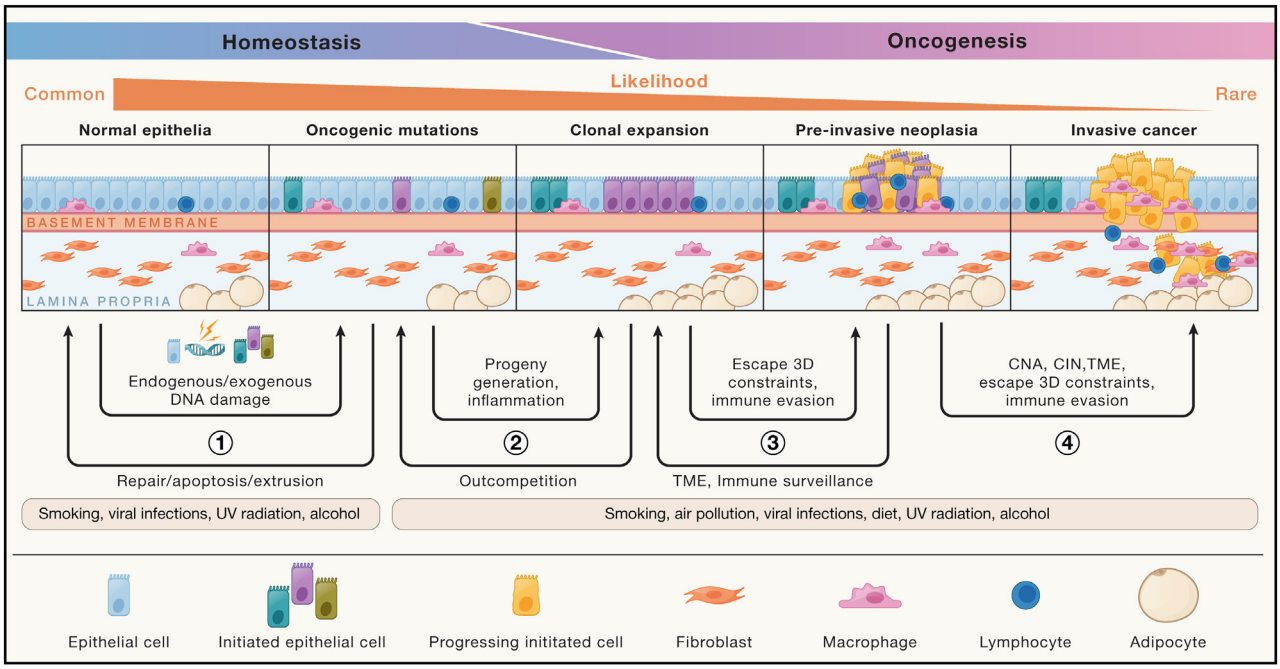

Figure 1. Multi-stage carcinogenesis within solid tumors as influenced by cancer risk factors

In homeostasis, epithelial sheets are surrounded by both structural and cellular microenvironmental support.

(1) Tumor initiation occurs when a cell gains a heritable alteration, typically an oncogenic driver mutation, either from endogenous or exogenous sources of DNA damage, the latter including smoking, viral infections, alcohol, and UV radiation. Initiated cells are then subject to selection pressures of the environment and compete with surrounding cells for space and resources to either persist in the tissue or are removed (repair, apoptosis, or extrusion). This somatic evolution is a function of homeostasis, given that initiated cells accumulate over time and are found in healthy tissues with no evidence of disease. (2) Initiated cells can either be removed from the tissue via both cell and non-autonomous processes ("outcompetition"), persist with no functional outcomes, or gain a selective advantage and proliferate. Cancer risk factors can alter the fitness landscape of the tissue to allow for initiated cell expansion (inflammation, progeny generation). (3) Clonal expansions of oncogenic cells can undergo further unrestrained growth to form pre-invasive lesions that distort the confines of the normal tissue architecture and evade immune detection. Not all lesions progress to invasive cancers, they can remain indolent or regress, aided by the microenvironment and immune surveillance. (4) The "oncogenic switch" comprises pre-invasive lesions that break tissue constraints to form invasive cancers and constitutes an irreversible process. This switch can involve chromosomal instability (CIN), leading to an accumulation of copy-number alterations (CNAs), and microenvironmental remodeling. Cancer risk factors can alter cell intrinsic and extrinsic factors in steps (3–4) to enable initiated cells to progress. It should be noted that cancer risk factors may affect tissues before the acquisition of oncogenic alterations and their non-mutagenic tumor-promoting roles can be imprinted upon the tissue. Also depicted is the likelihood of occurrence of each stage; invasive cancers are exceedingly rare relative to the occurrence of mutant clonal expansions within normal tissue.

be operating and that oncogenic driver mutations found in cancer may arise, not due to a carcinogen, but as a result of the natural aging process (reviewed in Evans and DeGregori[79]). This challenges our understanding of early tumorigenesis and necessitates a re-evaluation of tumor initiation. If little can be done to prevent the acquisition of oncogenic mutations in normal tissues with age, attention must be turned to addressing the mechanistic effects of modifiable risk factors acting upon these latent mutant cells to drive early cancer evolution.

Evidence is emerging that cancer risk factors may act by non-mutagenic mechanisms and confer selective advantage upon cells already harboring cancer-causing mutations: so-called cancer promoters (Glossary, Figure 1). This concept was first defined in a murine skin carcinogenesis model by Berenblum and Shubik, where tumors are "initiated" via topical application of the mutagen dimethylbenzanthracene (DMBA), later revealed to induce activating *Hras* mutations, which are insufficient to form tumors unless provoked to expand via subsequent application of croton oil, an inflammatory agent.[8,80,81] In these seminal studies, DMBA-initiated cells within the skin remained dormant for much of the lifespan of the mouse, but following croton oil treatment, papillomas robustly appeared after 2 months.[8] Even if oil was applied 1 year after creation of the mutant cells, it was still able to promote tumor formation.[82] Further evidence of tumor promotion has been gained from studies of normal rat mammary glands that contain oncogenic *Hras* mutations that spontaneously arise during development. Treatment with the carcinogen nitrosomethylurea (NMU) did not increase the number of these mutations but did elevate tumor formation.[83] Importantly, the *Hras* mutations that existed prior to NMU treatment did not invariably result in tumorigenesis; their oncogenic potential was only realized upon NMU exposure,[84] highlighting the potential for NMU to act as a promoter rather than an initiator of cancer. There is also evidence that the application of a promoter before the initiation of oncogenic drivers can enhance pancreatic tumorigenesis, indicating that the order of initiation and promotion may be interchangeable in some models.[85] This suggests that the effects of "promoters" may imprint upon tissue before the acquisition of the oncogenic driver mutation. A number of major cancer risk factors may act via a tumor promoting

Box 1.

The notion of the acquisition of cancer mutations being due to "bad luck" and resistant to prevention efforts was proposed by Tomasetti et al.,[21] where they suggest that over 60% of cancer is due to intrinsic, random DNA mutations arising from cell division. However, a large number of subsequent studies challenge this theory. Opposing perspectives to the "bad luck" theory put forward that mutations due to intrinsic errors in DNA replication in isolation cannot explain how all cancers begin. Mathematical modeling of the build up of such mutations rarely led to the development of cancer.[24] Moreover, cell divisions could be influenced by extrinsic factors: epidemiological evidence indicates that the lifetime risk of cancer is reduced if risk factors (such as smoking) are eliminated,[25] and individuals who migrated to geographical regions with higher rates of cancer incidence developed cancer at rates consistent with their new homes.[26,27] Recent studies suggest that 60%–90% of all cancers are due to non-intrinsic risk (i.e., exogenous and cell extrinsic risk factors) and therefore could be modifiable. This estimate varies by cancer type, with hematological cancers, such as acute myeloid leukemia and chronic lymphocytic leukemia, are less influenced by risk factors.[18] Acquiring an oncogenic alteration via bad luck may be but one step of tumorigenesis, yet this alteration must function within a permissive environment, resulting from the culmination of cell lineage, tissue architecture, and systemic factors to drive cancer formation.

mechanism and are summarized in Table 1. Research into tumor promoters has established four concepts: (1) promoters require a substrate for cancer development, typically a cell with an oncogenic driver mutation, that in some instances may be generated by the promoter itself; (2) tumor promoters may exert their effects either before or after the acquisition of the substrate; (3) exposure to the promoter is not continually required through cancer development, suggesting a "hit and run" mechanism that may be difficult to target; (4) promoters can act at multiple stages of tumor evolution (Figure 1). This review will focus upon understanding the molecular mechanisms by which the body restrains mutant cells from developing into a cancer, and conversely, how risk factors revise these processes to promote cancer. This knowledge could inform novel screening paradigms in high-risk, under-served populations and guide "molecularly targeted" cancer prevention approaches to inhibit cancer initiation.

HOW DOES THE BODY PROTECT AGAINST CANCER

Oncogenic driver mutations and genetic alterations are fundamental to tumorigenesis, as demonstrated by the success of targeted therapies for oncogene-addicted tumors.[86] Yet these genomic alterations must function within the cellular and tissue environment of the host that can inhibit cancer formation. Cancer risk factors can exploit these constraints upon tumor progression, and we have termed these mechanisms of action as "hallmarks of tumor promotion" (Figure 2). We now discuss the non-mutagenic mechanisms underlying susceptible cell lineages, progeny generation, cooperating inflammation, tissue takeover, escaping tissue restraints, and immune evasion as altered by risk factors, with the acknowledgment that cooperating genomic alterations also control the likelihood of oncogenesis.[14]

Cell lineage and tumorigenesis

A key determinant of tumor initiation is the characteristics of the first cell that acquires the genomic alteration resulting in cancer formation–known as the cell of origin or tumor initiating cell (Glossary). Hierarchical tissue organization and features linked to cell lineage, including DNA repair capabilities, cell cycle status, and chromatin architecture, underlie an individual cell's susceptibility to acquiring a mutation within its genome, a component of oncogenic competence[87] (Glossary) reviewed elsewhere.[88–93] We will focus on the ability of this cell to initiate cancer *after* the acquisition of an oncogenic driver, as these processes could prove reversible. Each acquired genomic lesion must operate within the pre-existing transcriptional and post-translational networks within a cell that governs its role within an organ, and these networks are not always permissive to tumor formation.[94] Identifying cell states susceptible to tumor initiation using lineage-defined mouse models, genetic engineering of normal cell organoids, or correlative analyses from sequencing data (cell of origin identification methods extensively reviewed in Visvader[95]), both under steady state conditions and as provoked by exposure to exogenous risk factors, will reveal the molecular determinants of, and potential prevention strategies against, cancer formation.

Adult tissue-specific stem and progenitor cells are likely candidates for tumor initiation due to their capacity for self-renewal, ability to produce daughter cells, and their relative longevity within tissues, thereby allowing for the acquisition of oncogenic lesions. Hyperactivation of the Wnt pathway via deletion of *Apc* in stem cells of the murine intestinal crypt leads to the formation of large adenomas that are not observed when the same deletion is restricted to transit-amplifying cells.[96] Similarly, the *Eml4-Alk* fusion drives murine lung adenocarcinoma from bronchiolar progenitor club cells as well as alveolar type II progenitor cells, yet more differentiated ciliated cells of the airways or alveolar type I cells are resistant to *Eml4-Alk*-fusion-driven tumorigenesis[97] (Table 2). However, in some tissue- and genomic-lesion-dependent contexts, stem/progenitor cells are impervious to transformation. Inactivation of the tumor suppressors *Rb1* and *Trp53*—driver lesions of small cell lung cancer—within rare neuroendocrine airway cells results in small cell lung cancer formation, while club or alveolar type II progenitor cells are either refractory to this transformation or have low tumor penetrance.[98] Dedifferentiation of mature, pigment-producing melanocytes were the initiating cells of *Braf-V600E*-driven, *Pten*-deficient melanoma, whereas melanocyte stem cells in the hair follicle bulge did not form tumors[99] (Table 2). Different oncogenic drivers activated within the same initiating cell lineage result in tumors of divergent subtypes; lung club cells and alveolar type II cells can give rise to lung squamous cell carcinoma driven by *Pten*, *Cdkn2ab* loss, and *Sox2* overexpression.[100] These cells can also generate lung adenocarcinoma driven by exposure to urethane[101] via genetic activation of *KrasG12D* mutation[102] or by *Eml4-Alk* fusions mentioned above,[97] demonstrating remarkable plasticity (Table 2). Hence, the activation of oncogenic drivers can be insufficient to initiate cancer if they occur in a non-permissive cellular context, and the combination of cell identity and oncogenic driver alter the phenotype of the resulting lesion.

Table 1. Exogenous cancer risk factors associated with enhanced incidence of particular cancers and proposed non-mutagenic mechanisms by which they promote tumor initiation

Exogenous risk factor	Associated cancer type	Non-mutagenic tumor promotion mechanism
air pollution	lung, bronchus, trachea	macrophage release of IL-1β; aberrant thickening of ECM and impaired adaptive immune response[28,29,30]
asbestos	mesothelioma	macrophage release of IL-1β via NLRP3 inflammasome[31]
tobacco smoking	oral cavity, pharynx; esophagus; stomach; colorectum; liver; pancreas; nasal cavity; larynx; lung, bronchus, trachea; cervix; kidney; renal pelvis; ureter; urinary bladder; acute myeloid leukemia	IKKβ/NF-κB dependent production of cytokines in lung myeloid cells; gut microbial dysbiosis, enhanced oncogenic MAPK signaling and impaired gut barrier function[32,33]
secondhand smoke	lung, bronchus, trachea	impaired adaptive immune response and elevated inflammation[34]
excess body weight/poor diet	esophagus; stomach; colorectum; liver; gallbladder; pancreas; female breast; corpus uteri; ovary; kidney, renal pelvis; thyroid; multiple myeloma; oral cavity, pharynx, larynx; lung, bronchus trachea	activation of oncogenic Kras via COX2 and inflammation in the pancreas; suppressed extrusion of oncogenic cells; interstitial breast fibrosis alters ECM; reduced T cell competency, enhanced cell stemness and progeny generation[35–43]
alcohol intake	lip, oral cavity, pharynx; esophagus; colorectum; liver; larynx; female breast	perturbed estrogen and plasma insulin-like growth factor; decreased $CD8^+$ T cells and elevated macrophages[44,45]
ultraviolet radiation	melanoma of the skin	induced migration and proliferation of oncogenic melanocytes; impaired adaptive immune response[46,47]
HPV infection	cervical cancer, head and neck cancers	inflammation[48]
Helicobacter pylori infection	gastric cancer	perturbed E-cadherin/β-catenin complex inducing transdifferentiation[49]
chronic hepatitis B/C infection	liver cancer	inflammation and fibrosis with elevated cytokines and chemokines[50]
Epstein-Barr virus	lymphoma; nasopharyngeal cancer; gastric cancer	aberrant methylation[51]

Mechanisms permitting lineage-dependent oncogenesis

Why do oncogenic drivers activated in different cell lineages exhibit such divergent behaviors? Features underlying lineage commitment, including cell fate (self-renewal, progeny generation, differentiation, apoptosis, or senescence) and associated chromatin/transcriptional states, govern this cell intrinsic oncogenic competence. Hair follicle stem cells are unable to initiate *KrasG12D*, *Trp53*-deficient skin squamous cell carcinomas if these alterations are induced during the Pten-dependent quiescent phase of the hair cycle (Table 2).[103] In contrast to basal stem cells, committed epidermal progenitor cells cannot generate aberrant Hedgehog-driven basal cell carcinomas due to reduced cell proliferation rates and greater sensitivity to p53-mediated apoptosis.[104] The mechanism preventing epidermal progenitor cells from initiating oncogenic *Pik3ca*-driven skin squamous cell carcinomas is neither via enhanced cellular senescence nor apoptosis but by skewing *Pik3ca* progenitor cell differentiation into cells that are shed from the epithelium,[108] also a mechanism noted in *Hras-G12V*-driven tumorigenesis.[109,110]

In multiple organs, Prominen-1 (Prom1) marks stem/progenitor cells capable of giving rise to various experimentally induced oncogene and tumor suppressor-driven cancers. The key determinant of oncogenic competence was the generative capacity of a given Prom1+ cell, that is, the number of lineage-marked progeny a cell could produce in the steady state.[111] Lineage-specific transcription factors and chromatin-modifying enzyme expression govern hair follicle and melanocyte stem cell permissiveness to tumorigenesis within *BRAF-V600E* and *KrasG12D*-driven melanoma and squamous cell carcinoma, respectively,[87,112] likely through generating chromatin states that enable epithelial-to-mesenchymal transition. These results are significant in that a recent DNA methylation analysis of 39 cell types from healthy patient tissue samples shows that cells of the same lineage harbor 99% identical methylomes across patients.[113] This result indicates that a deep understanding of oncogenic competence relative to epigenomic state could help predict the likelihood of tumorigenesis. Unique transcriptional programs associated with the anatomical position of melanocytes also determined their ability to initiate cancers driven by *CRKL* amplifications, an alteration unique to patient acral melanomas.[114]

Box 2.

One of the major questions in cancer research concerns the oncogenic-switch; that is, the molecular mechanisms that convert a pre-invasive lesion to an invasive carcinoma. Incidental detection of pre-invasive and non-progressing cancers in autopsy studies have demonstrated that tumors can arise early; for example, in the prostate, 5% of autopsies of people less than 30 years old were found to have cancer, rising to 59% in people over 79 years old.[10] In the breast, the estimated prevalence of incidental cancer and early lesions was 19.5%.[11] In a seminal paper, Vogelstein et al.[67] correlated sequentially occurring somatic genomic alterations to histological features and the adenoma to adenocarcinoma transition in colorectal cancer. Inactivation of *APC*, an initiating step in colorectal cancer[68] is followed by *KRAS* mutation, 18q loss, and *TP53* mutation and/or loss.[69] The adenoma-to-carcinoma transition is thought to coincide with 18q loss and an increase in chromosomal instability.[70] These observations are partially recapitulated by stepwise CRISPR-Cas9-mediated introduction of oncogenic alterations within *APC*, *KRAS*, and *TP53*, as well as additional alterations in *SMAD4* (residing on 18q) and *PIK3CA* (commonly mutated in colorectal cancer) in healthy colorectal organoids. The engineered organoids exhibited growth factor-independent proliferation but were non-invasive, chromosomally stable, and displayed adenoma-like histology upon transplant, until the spontaneous acquisition of additional chromosomal instability allowed for invasive properties.[71] Work studying the genomic progression of pre-invasive breast cancer lesions to ductal carcinoma *in situ* (DCIS) and the arising invasive disease revealed a very high concordance of both driver mutations and chromosomal amplifications in pre-invasive and invasive lesions, suggesting that non-genomic and microenvironmental changes permit an oncogenic switch.[72,73] Analysis of progressing and regressing lung squamous cell carcinoma *in situ* revealed that regressive lesions displayed epigenetic and transcriptional profiles that resembled normal bronchial epithelium, whereas progressing carcinoma *in situ* lesions displayed high chromosomal instability but no additional oncogenic drivers.[74] Although these data indicate that the adenoma to carcinoma switch is initiated by copy-number alterations and chromosomal instability, in a subsequent study, the authors expanded their analysis to demonstrate that mutations and copy-number aberrations in genes involved in immune modulation were more prevalent in progressive than regressive lesions,[75] hinting that additional cell-extrinsic mechanisms might be involved in the adenoma to carcinoma transition. These data suggest that some DNA aberrations required for carcinogenesis are acquired at the earliest stages of tumor initiation and that other factors—likely both cell intrinsic and extrinsic—control the progression to invasive disease.

Hence, diverse molecular pathways govern competence to initiate tumors, each intricately linked to cell lineage.

Cancer risk factors impact lineage fidelity

The studies mentioned above address tumor initiation within tissue homeostasis, and there are a plethora of studies demonstrating that the oncogenic competence of cells is unequivocally altered by a diverse range of exposures, injuries, and systemic challenges that promote cancer. Cancer risk factors generate new selective pressures that can either allow for new cancer-permissive states in cells with no previous initiating capacity or accelerate tumorigenesis in cancer-susceptible lineages (Table 2). These cell-state changes are provoked by two central mechanisms: by altering local or systemic inflammation or changing hormone levels, ultimately overcoming the forces protecting against initiated cell expansion (Figure 2).

Quiescent melanocytes are resistant to *Pten*-deficient, *BRAF*-driven transformation in the steady state,[99] yet when exposed to UV radiation, these oncogenic melanocytes migrate to the epidermis, proliferate, undergo hyperpigmentation, and form invasive melanomas, regardless of the initiating stem cell cycle stage[46] (Figure 2; susceptible cell lineage, progeny generation, escape 3D constraints). Treatment with sunscreen or the anti-inflammatory steroid dexamethasone during UVB exposure inhibited this migration (Figure 2; cooperating inflammation), highlighting that oncogenesis can be preventable. Similarly, pancreatic insulin-expressing endocrine cells, harboring mutant *Kras*, only undergo transdifferentiation to form neoplasms when mice are pretreated with caerulin, a cholecystokinin analog that models injury similar to pancreatitis[105] (Figure 2; susceptible cell lineage). Caerulin also accelerates *Kras* tumorigenesis derived from pancreatic acinar cells.[106] Within acinar cells, caerulin treatment synergizes with *Kras* mutations to provoke rapid epigenetic remodeling, allowing for enhanced expression of the epithelial alarmin IL-33 that drives neoplastic gene expression programs.[115] Suppression of the epigenetic modulator BRD4 prevented the appearance of the caerulin and mutant *Kras*-driven pre-invasive lesions. Caerulin-exposed acinar cells retain an IL-6 mediated memory of inflammation and damage and are subsequently primed for tumorigenesis, undergoing a rapid metaplasia to neoplastic transformation upon later activation of *Kras* mutation despite long-term resolution of the initial injury[85] (Figure 2; cooperating inflammation). We have recently identified that exposure to air pollution results in IL-1β release from lung macrophages, resulting in enhanced alveolar type II cell progenitor activity that fuels adenocarcinoma initiation if the alveolar type II cells harbor an oncogenic mutation in *EGFR*[28] (Figure 2; cooperating inflammation, progeny generation, susceptible cell lineage). These non-mutagenic mechanisms of tumor promotion are reported in models of *H. pylori* infection and gastric cancer,[49,116] asbestos exposure and mesothelioma,[117] smoking and lung adenocarcinoma,[32] and obesity and liver cancer,[118] as well as colorectal cancer,[119] summarized in Table 1. Thus, a central paradigm by which cancer risk factors promote tumor formation is by causing microenvironment-derived inflammation, resulting in dysregulated differentiation programs within epithelial cells to tip the scale toward carcinogenesis. In many cases, the inflammatory state is preventable, rendering cancer initiation in susceptible tissues clinically targetable[28,46,118] (Table 2).

Excess body weight and obesity is associated with an increased risk of cancer in at least 13 anatomical sites and is linked with altered systemic and local factors beyond inflammation. Peripheral adipose tissue is a site of estrogen production with estrone levels around 2-fold higher in obese women.[120,121] Estrone supplementation increased the number of murine tumor-initiating stem cells, promoting the growth of syngeneic estrogen receptor positive mammary tumor models[39] (Figure 2; progeny generation). Co-culture of adipocytes and breast cancer cells upregulates inflammatory cytokines to increase stemness within cancer cells[40] (Figure 2; susceptible cell lineage). High-fat diets can also alter bile acids, the gut microbiome,

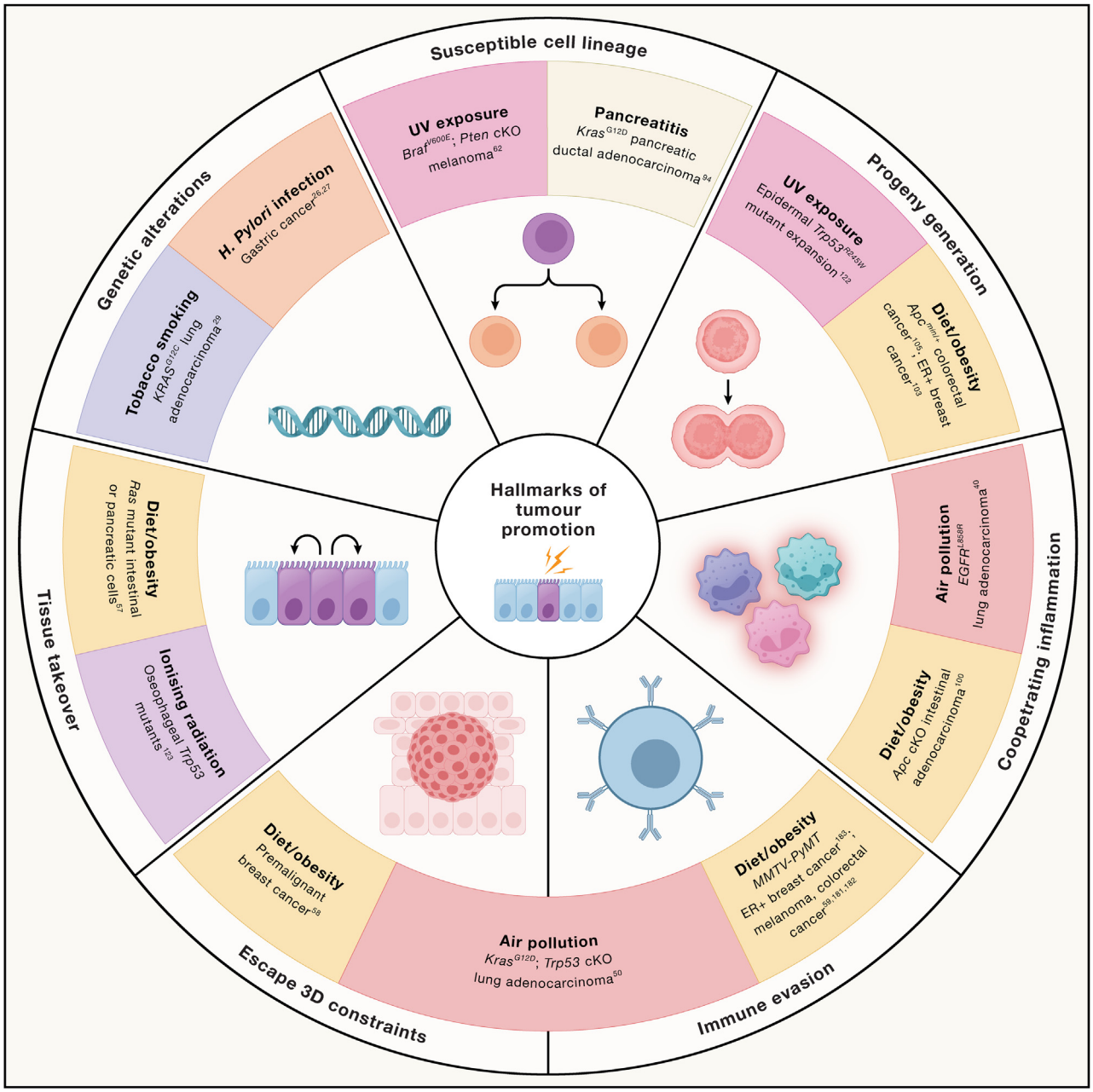

Figure 2. Mechanisms of action for cancer risk factors

Cancer risk factors can facilitate cancer formation by multiple mechanisms. While some risk factors can induce genetic alterations that both initiate and aid tumor progression, here, we focus on six non-mutagenic mechanisms of tumor promotion and examples of risk factors that function via these axes. Cancer risk factors may function in concert and at many stages of the oncogenic process and do not necessarily act in a defined temporal fashion. Understanding these mechanisms and the relationship between exposure duration and cancer risk will identify individuals in danger of developing cancer and reveal potential preventative therapeutic avenues. cKO, conditional knockout.

and digestive hormones to promote colorectal and pancreatic cancers,[41–43] demonstrating the diverse signaling pathways in which cancer risk factors can increase the likelihood of tumor formation. Research to identify the precise molecular mechanisms, by which initiating cells are perturbed by exogenous risk factors, may reveal novel therapeutic targets for curtailing their malignant transformation, yet preserving essential tissue regeneration.

Cell competition and homeostasis

Acquisition of oncogenic mutations can either enhance or diminish the cellular fitness of the mutant cell (Glossary). In the

Table 2. Mouse models of tumorigenesis in the lung, skin, and pancreas that restrict genomic drivers of cancers to specific cell lineages, as influenced by model cancer risk factors

	Cell lineage	Genetic driver	Tumor outcome	Tumor outcome with cancer risk factor
lung	club	*Eml4-Alk* fusion	adenocarcinoma[97]	–
	club	*KrasG12D* +/− *Trp53* cKO	adenocarcinoma[102]	smoking promotes tumors[32]
	club	*Rb1*;*Trp53* cKO	no tumor[98]	–
	club	*Pten*;*Cdkn2ab* cKO, *Sox2* OE	squamous cell carcinoma[100]	–
	neuroendocrine	*Rb1*;*Trp53* cKO	small cell lung cancer[98]	–
	ciliated cell	*Eml4-Alk* fusion	no tumor[97]	–
	alveolar type I	*Eml4-Alk* fusion	no tumor[97]	–
	alveolar type II	*Eml4-Alk* fusion	adenocarcinoma[97]	–
	alveolar type II	*KrasG12D* +/− *Trp53 cKO*	adenocarcinoma[102]	smoking, air pollution promotes tumors[28,32]
	alveolar type II	*huEGFR-L858R*	adenocarcinoma[28]	air pollution promotes tumors[28]
	alveolar type II	*Rb1*;*Trp53* cKO	50% penetrance small cell lung cancer[98]	–
	alveolar type II	*Pten*;*Cdkn2ab* cKO, Sox2 OE	squamous cell carcinoma[100]	–
skin	pigment-producing melanocytes	*Braf-V600E*; *Pten* cKO	melanoma[99]	–
	hair follicle melanocyte stem cells	*Braf-V600E*; *Pten* cKO	no tumor[99]	UV promotes tumors[46]
	epidermal stem cell	*KrasG12D* +/− *Trp53* cKO	squamous cell carcinoma[103]	–
	epidermal stem cell	*SmoM2* OE	basal cell carcinoma[104]	–
	epidermal transit amplifying cells	*KrasG12D* +/− *Trp53* cKO	no tumor[103]	–
	epidermal transit amplifying cells	*SmoM2* OE	no tumor[104]	–
pancreas	acinar	*KrasG12D/V*	PDAC*[105,106]	caerulin promotes tumors[105,106]
	acinar	*KrasG12D* + *Trp53* cKO	PDAC[107]	–
	ductal	*KrasG12D*	no tumor[107]	–
	ductal	*KrasG12D* + *Trp53* cKO	PDAC[107]	–
	islet (endocrine)	*KrasG12D*	no tumor[105]	caerulin promotes tumors[105]

cKO, conditional knockout; OE, overexpression; PDAC, pancreatic ductal adenocarcinoma. *Adult acinar cells less competent.

latter case, ''cell competition'' can limit clonal expansions of the mutant cells in the epithelial sheet (Figure 1). While less fit cells may be viable in isolation, when in contact with fitter cells, they are outcompeted. ''Fitness'' is a relative, context-dependent state and can be influenced by cell-extrinsic factors, where cells of inferior fitness in one situation may prove superior in another.[122] Elimination of oncogenic cells in cell lines and mouse models can proceed via apoptosis and cell extrusion (Figure 1, step 1). For example, it was demonstrated that when mosaic recombination of *HRasG12V* was induced in murine intestinal and colorectal cells by a low-dose tamoxifen, transformed cells were extruded from intestinal organoids and intestinal epithelium *in vivo* when surrounded by wild-type neighbors. The sporadically transformed cells exhibited mitochondrial membrane dysfunction, changing the metabolic state of the mutated cell. The change in metabolic state was further exacerbated by the surrounding normal cells and promoted extrusion of the mutated cell from the monolayer.[123] In mouse models of Notch- and Akt-driven liver tumors, scattered initiated cells are surrounded by adjacent normal epithelia and activate Hippo signaling within these healthy cells in a paracrine manner.[124] Deletion of the transcription regulators *Yap* and *Taz* in peritumoral normal hepatocytes promoted tumor growth, whereas hyperactivation of YAP in neighboring normal cells was sufficient to drive regression of liver tumors, demonstrating the key role wild-type epithelia play in protecting against tumor initiation[124] (Figure 1, steps 1 and 2). Outcompetition of *Kras* mutant cells by normal neighbors has also been reported in mouse pancreas including from the acinar, ductal, and endocrine compartments, where Epha2 signaling is essential for controlling cell elimination via loss of cell-cell adhesions.[125] *Kras* mutant cells upregulate EphA2 which is sensed in the normal epithelia and triggers repulsion of mutant cells. It has also been proposed that a ''fitness fingerprint'' on cancer cells allows detection by the surrounding epithelia. Combinations of *Flower* gene isoforms on the cell membrane can indicate fitness levels and mediate cell

competition via cell-cell contacts leading to apoptosis.[126] In the hair follicle, wild-type cells are required for the clearance of oncogenic cells driven by either activated Wnt signaling or HRasG12V to preserve homeostasis.[127] Here, the deformation of skin tissue architecture is a key driver of regression of oncogenic lesions. Epithelial tension is critical for cell extrusion and the expression of e-cadherin on normal surrounding cellscontributes to mutant cell extrusion.[128] Additional cytoskeletal rearrangements in the surrounding normal cells, such as filamin and vimentin accumulation, also contribute to this process.[129] Additional triggers and initiators of coordinated extrusion of mutant cells are still an ongoing area of research. For instance, $HRas^{G12V}$ cells can initiate calcium wave propagation across surrounding cells, triggering polarized movement and facilitating extrusion.[130,131] Although further research into these processes in human tissue is needed, the data discussed above highlight how cell competition within an epithelium may eliminate sporadic oncogenic cells that might otherwise go on to form a tumor.

Cell competition and clonal expansions

Mutant cells with increased fitness exploit cell competitive processes to expand. Positively selected mutations can act by either intrinsically increasing the growth advantage of the cell or through paracrine signaling upon adjacent wild-type cells. In the mouse intestine, *Apc*-null stem cells secrete the Wnt inhibitor NOTUM, which prompts wild-type neighboring cells to differentiate, producing space for mutant cell colonisation.[132,133] As the *Apc* mutation activates WNT signaling downstream of the secreted NOTUM antagonist, mutant cells are not inhibited and can achieve tissue takeover (Figure 1, steps 2 and 3). In the mouse esophagus, *Notch1* mutant cells can activate Notch signaling within adjacent wild-type neighbors, inducing differentiation and removal from the stem cell niche thereby allowing space for mutant cell expansion.[134] These data highlight that particular mutant cells can outcompete neighbors by capitalizing on their own genomic alterations to create space and colonize epithelial tissues. More research is necessary to determine the precise molecular mechanisms that control these processes to potentially uncover preventative strategies against mutant cell expansion.

Cancer risk factors alter tissue takeover

The selective advantage of cell phenotypes is not always cell autonomous and hence can be altered. For example, in the mouse epidermis, lineage tracing of cells harboring a $Trp53^{R245W}$ mutation expanded and colonized the epidermis up to 24 weeks post induction. The colonization may occur via a bias in mutant progeny, with mutant cells producing more progenitor daughter cells than differentiated daughter cells.[135] However, beyond 24 weeks, the rate of *Trp53* mutant cell expansion slowed, suggesting the progeny cell fate imbalance is not fully cell autonomous but also responds to external cues. Addition of a low-dose UV-exposure challenge was found to accelerate *Trp53* mutant cell colonization (Figure 2, tissue takeover, progeny generation); however, longer term (9 months) of UV exposure led to *Trp53* mutant cell depletion. It has been proposed that long-term UV exposure generates other mutant cells that can outcompete the lineage-traced *Trp53* mutant cells[135] (Figure 2, genetic alterations). In another study, altering oxidative stress in the esophagus via low-dose ionizing radiation (LDIR) demonstrated that *Trp53* mutant cells are resistant to LDIR, allowing them to outcompete wild-type neighbors after exposure (Figure 2, tissue takeover, progeny generation). Combining LDIR and the antioxidant N-acetyl-cysteine increases normal cell fitness leading to elimination of *Trp53* mutant cells in the esophagus by shifting the outcome of proliferation, with mutant cells less likely to produce proliferating progeny.[136] Diet may also alter cell competition dynamics. For instance, the ability of *Apc*-null cells to takeover an intestinal crypt is reduced by a calorie-restricted diet due to increased numbers of competing wild-type stem cells,[137] and a high-fat diet may inhibit extrusion of oncogenic *Ras* mutant cells[36] (Figure 2, tissue takeover). Finally, in the mouse esophagus, *Notch1* mutant clones can outcompete and eliminate early tumors through cell competition. Treatment with the Notch signaling inhibitors can increase fitness across the tissue and prevent the out-competition of tumors by *Notch1* mutant clones.[138,139] Together, these data demonstrate how environmental factors and pharmacological intervention can utilize cell competition pathways to promote or inhibit mutant cell expansion.

These studies establish that epithelial sheets have evolved to sense and eliminate deleterious cells to protect against tumor formation. They also highlight the need to study mouse models of tumor initiation where sporadic oncogenic cells are surrounded by wild-type neighbors, as opposed to models where oncogenes/tumor suppressors are expressed at supraphysiological levels in many cells. Tissue homeostasis perturbation by cancer promoters alters selective pressures differentially in mutant and wild-type neighbors and can preferentially promote the expansion of mutant cells, thus beginning the initiating stage of oncogenesis.

3D tissue architecture constrains oncogenesis

Healthy epithelial tissues tightly balance the production and loss of cells, which may underlie the observed tissue constraints on tumor initiation. For example, epithelial cells respond to mechanical cues, and cell-cell contacts can regulate proliferation. Contact inhibition of cell growth has been proposed to occur via e-cadherin-mediated cell contacts and the Hippo pathway,[140] allowing epithelia to act in a coordinated fashion at the tissue level.[141] Some oncogenic transformations promote the escape from contact inhibition. One study using 3D culture of the non-transformed mammary epithelial cell line MCF10A found that sporadic expression of oncogenic drivers that either promote proliferation (cyclin D1), deregulate Myc, or activate AKT signaling resulted in mutant cells that remained quiescent within the acini, provided they were surrounded by wild-type neighbors (Figure 1, step 1). In contrast, *ERBB2* single-mutant MCF10A cells escaped the epithelial monolayer and proliferated, a process dependent on matrix metalloproteinases expression within the *ERBB2* mutant cell[142] (Figure 1, steps 2 and 3). Similar phenomena have been observed in mouse models of intestinal tumorigenesis, whereby Eph-ephrin signaling between mutant and the surrounding normal epithelia was found to compartmentalize adenomas and suppress tumor progression.[143] Epithelial tissues have an organized 3D structure; for example, the

intestine consists of protruding finger-like villi and basal crypts, whereas the epithelium of the skin is stratified into multiple layers of epithelial cells. This higher order structure can also play a role in the likelihood of tumor initiation. There are a limited number of stem cells within intestinal crypts, and a particular clone can colonize the entire crypt, generating a monoclonal unit. Oncogenic mutations, such as *Apc* loss or *Kras* activation, give stem cells a competitive advantage in this process and increase the likelihood they will achieve monoclonality within the crypt.[144] Crypt fission can allow spread of mutant cells from monoclonal mutant crypts over the wider epithelium, and in line with this, areas of *KRAS*-mutated crypts have been observed adjacent to colorectal cancer in humans.[145,146] In contrast, it has been hypothesized that crypt fusion has the potential to reintroduce competing wild-type stem cells to a mutant crypt, restart competition, and potentially eradicate mutant cells.[147]

In the epidermis, progenitors proliferate at the lower layer of a stratified epithelium and commit to differentiation and travel upwards to replenish the skin barrier. While in monolayers, proliferation and cytoskeletal contractility are key determinants of tissue architecture; in the stratified epidermis it appears that mechanical forces arising below from the basement membrane and above from the stratification and differentiation of cells underpin pre-malignant tumor formation and progression.[148] Indeed, genetically decreasing the stiffness of the basement membrane was found to promote the progression of *HRasG12V*-driven squamous cell carcinoma (Figure 1, steps 3 and 4). This highlights how sporadic mutant cells arising in complex tissues have context-dependent fates that can be governed by 3D structure and associated arising forces.

Cancer risk factors alter 3D tissue structure

The structure of tissues does not only arise from epithelial cells but also from dynamic interaction between structural components, such as extracellular matrix (ECM) and cells from hematopoietic, mesenchymal, and endothelial lineages. This microenvironment can both restrict and promote early tumorigenesis. Transformed fibroblasts, when co-transplanted into athymic mice with one of several epithelial tumor cell lines (prostate, breast, and bladder), which do not form tumors alone, are sufficient to confer a tumor-initiating phenotype upon the cell line.[149] Destruction of the basement membrane in the mouse mammary gland leads to aberrant stroma and tumor formation.[150] TGF-beta receptor deletion within fibroblasts in genetically engineered mice is sufficient to induce epithelial tumors but only within the prostate and forestomach, although the genetic alterations of the arising tumors are unclear.[151] Fibroblasts can exert contractile forces on cancer cells[152] and the basement membrane[153] but also regulate the ECM.[154] There are several studies providing supporting evidence that the ECM can revert malignant epithelia to a more differentiated phenotype, potentially promoting regression.[155,156] Higher order interactions have also begun to be characterized, with macrophages being able to secrete lysyl oxidase (LOX) enzymes that stiffen the stroma by promoting crosslinking in the ECM, a process that is associated with more aggressive mammary tumor cell behavior.[157] In line with this, greater breast density measured by mammogram is associated with enhanced risk of breast cancer.[158] Obesity can promote fibrosis, increase ECM stiffness, and promote expansion of the breast epithelial cell line MCF10A[37] (Figure 2, escape 3D constraints). In the lung, elastin fibers play a critical role in alveolar structure and can be broken down by neutrophil-derived elastase. Elastase is inhibited by alpha-1 antitrypsin and patients with alpha-1 antitrypsin deficiency not only have an elevated risk of emphysema, resulting in microenvironment changes, but also a marked increased risk of lung cancer independent of tobacco exposure[159] (Figure 2, escape 3D constraints). Alterations to the ECM offer potential therapeutic targets with inhibition of LOXL2, a collagen and elastase crosslinking enzyme, reducing fibrosis, cross-linked collagen, and breast cancer tumor growth.[160] Altogether, this highlights how tissue architecture can restrain the earliest stages of cancer with tissue architecture disruption able to promote cancer in mouse models.

Adaptive immunosurveillance and tumor control

Adaptive immune surveillance was first proposed by Erlich in 1909,[161] then expanded by Burnet in 1957 in the theory that T lymphocytes conducted tissue immunosurveillance to protect the host against cancer.[162] Burnet proposed that nascent cancer clones could express non-self antigens, thus providing the potential to be recognized and eliminated by cytotoxic T cells, thereby preventing tumor initiation. The interplay between the adaptive immune system and a tumor is thought to occur via three different mechanisms: elimination via depletion of antigenic nascent tumor clones, equilibrium where further expansion of initiated cells is restrained by host immune cells, and finally, escape where tumor cells with lower immunogenicity or with the capacity to restrain immune responses grow into invasive lesions.[163] Cancer immunosurveillance is coordinated by circulating and tissue-resident adaptive and innate immune cells within each organ and is altered via endogenous and exogenous forces changing the selective pressure necessary for tumor initiation. Here, we will focus on the mechanisms by which adaptive immunity affects the growth of initiated cells, with a focus on functional studies in autochthonous models of epithelial cancers, and how these processes can be altered by exogenous risk factors.

The elimination of spontaneously arising antigenic tumor clones by host immunity is difficult to observe using patient data, and also challenging to detect in autochthonous mouse models. Yet we can infer that there is immune protection against cancer formation via the simple fact that immunocompromised individuals have higher incidences of certain, often virally induced, cancers[163] and the development of spontaneous tumors, including adenocarcinomas of the intestine and lung, in aged T cell deficient mice in contrast to immunocompetent mice (reviewed in Swann and Smyth[164]). These results imply that immunocompetent individuals restrain or reject oncogenic lesions more efficiently. There are many transplant studies of rejection of syngeneic tumor cell lines in immune-competent but not immunocompromised mice (reviewed in Schreiber et al.[163]). Transplant studies of cutaneous melanoma engineered to express a model neoantigen demonstrated tumor-specific tissue resident memory T cells could maintain cancer-immune equilibrium and protect the host from tumor growth.[165] Similarly, an organotypic transplant model of *Kras* mutant, *Trp53*-deficient

keratinocytes together with surrounding microenvironmental cells into immunocompetent hosts results in tumor rejection or prolonged periods of delayed squamous cell carcinoma initiation. This "equilibrium phase" correlated with initiated cells residing within hair follicles, suggesting that cell extrinsic mechanisms may also impair effective immune surveillance.[166] A proportion of pre-invasive lesions of patient lung squamous cell carcinoma (~40%) spontaneously regress, a phenomenon associated with the presence of infiltrating $CD8^+$ T cells in the epithelial lesion compared to those that progress.[75] In invasive patient lung adenocarcinomas and squamous cell carcinomas, neoantigens were less likely to occur in consistently expressed genes. This reduction in expressed neoantigens was strongest in highly immune infiltrated tumors compared to lowly infiltrated tumors, suggesting negative selection against antigenic clones.[167] Collectively, despite the difficulty in experimentally proving immunoediting and subsequent rejection, there is strong evidence that intact host immune responses can restrain and in some cases reject the outgrowth of malignant clones harboring potentially immunogenic somatic mutations.

Adaptive immune evasion and tumor progression

Why doesn't seemingly healthy tissue replete with cells harboring antigenic mutations attract T cell infiltrates capable of eliminating these mutant clones? There was no evidence of immune editing against healthy urothelial cells harboring putative antigenic mutations despite these cells carrying more than 500–2,000 mutations per genome by middle age.[168] This could be due to lower mutational burdens on average in healthy cells compared to their corresponding cancers,[59,168–170] yet it is also likely dependent on the nature of the clonal expansion—that is, the fraction of antigenic cells within the clone must reach a sufficient size to trigger an anti-tumor immune response. In a transplant study, murine leukemic cell lines encoded with known immunogenic peptides were readily rejected when subcutaneously transplanted into immunocompetent hosts at high cell numbers.[171] However, when these highly immunogenic clones were mixed within non-immunogenic tumor cells at low clonal fractions (250–650 cells per 5 million cells), these immunogenic clones were able to evade T cell mediated elimination from the larger polyclonal mix.[171] Mouse models of melanomas, liver, or kidney tumors engineered to express model neoantigens demonstrate that low levels of immunogenic peptide in early tumorigenesis induce T cell tolerance and result in anergic T cell responses against eventuating tumors.[172–175] Thus, cancer cells with immunogenic peptides can go undetected and form lesions if they are present at low fractions (Figure 1, step 4), demonstrating that neoantigen intratumour heterogeneity affects immune responses. This is also supported by observations in patients, where the presence of clonal neoantigen(s) in lung cancers—those expressed by every tumor cell in the clone—predict favorable response to checkpoint immunotherapies compared to patients harboring more heterogeneous tumors with largely subclonal neoantigens.[176–178] An inducible streptomycin-tagged mouse major histocompatibility complex (MHC) class I allele allows for the detection of class-I-bound peptide antigens *in vivo*, known as the immunopeptidome, and revealed largely shared immunopeptidomes between healthy lung alveolar type II cells and early *KrasG12D*, *Trp53*-driven lung adenocarcinomas. Only later-stage tumors had differential peptide presentation, further indication that there are insufficient neoantigens in early tumorigenesis required for tumor rejection.[179] Hence, the low abundance and heterogeneity of tumor antigens in early tumorigenesis likely aids immune evasion of nascent tumors.

Tumors may not need to "escape" immune predation to begin malignant transformation if they have sufficiently low antigenic properties, typically associated with low mutational burdens,[180,181] and are therefore not immunologically distinguishable from self. For example, a *Kras* mutant; *Trp53*-driven model of pancreatic cancer can be readily rejected when engineered to express an experimental neoantigen. Yet, without this neoantigen, it has a low tumor mutational burden, develops at similar rates in the presence or absence of T cells, and is resistant to checkpoint immunotherapy, indicating a lack of immune recognition due to absent neoantigens.[182] In contrast, some highly immunogenic tumor clones must develop mechanisms to avoid immune predation before forming an invasive cancer.[183,184] In models of *Kras*-driven lung adenocarcinoma or pancreatic cancer engineered to express the ovalbumin peptide, loss of MHC class I expression or the neoantigen were necessary for tumors to form.[185,186] Indeed, in many human tumors, evidence of immune evasion via expression of immune checkpoints and immunosuppressive signaling is observed in high-grade, pre-invasive lesions before the progression to invasive cancers;[187–189] in addition, loss of clonal neoantigens and antigen-presenting machinery in invasive lung cancers have been observed.[167] These results demonstrate that the pressure for cancers to become immunologically silent is highly selected in tumor initiation and progression to invasive cancers (Figure 1, step 4).

Cancer risk factors alter adaptive immunity

Understanding how immunosurveillance both protects against tumor initiation and also applies selective pressure to nascent-initiated cells allows us to tease apart an additional mechanism(s) by which exogenous risk factors enable carcinogenesis. UV radiation results in an immunosuppressive skin microenvironment via cytokine release and interfering with antigen-presenting cells, resulting in reduced ability to reject immunogenic tumors (reviewed in Hart and Norval[47]; Figure 2, cooperating inflammation and immune evasion). Inhaled air pollutant particulate matter adsorbs the enzyme peroxidasin, resulting in thickening of the alveolar matrix. This structural remodeling then limits $CD8^+$ T cell immune surveillance and promotes *Kras* mutant, *Trp53*-deficient lung adenocarcinoma formation[29] (Figure 2, escape 3D constraints and immune evasion). Pollutant-laden macrophages accumulate within human lung draining lymph nodes with age and disrupt T and B cell follicles,[30] highlighting that risk factors can alter local and systemic environments, resulting in inflammageing and failed cancer immunosurveillance (reviewed in Weisberg et al.[190] and Møller et al.[191]; Figure 2, immune evasion). High-fat diets in mouse models reduce T cell competency against transplanted and autochthonous models of melanoma, breast, and colorectal cancers through altered leptin signaling and excess lipid availability in the microenvironment that drives metabolic dysregulation and dysfunction within

$CD8^+$ T cells[38,192–195] (Figure 2, immune evasion). Caloric restriction can somewhat rescue cytotoxic T cell responses, where fasting results in T cell trafficking to the bone marrow to promote T memory cell responses to transplanted melanomas.[196] In contrast, risk factors can augment T cell activity, yet still indirectly promote tumorigenesis via premature T cell exhaustion or the rapid development of immune evasion mechanisms by tumor cells. Dysbiosis of gut microbiota primes for hyperstimulated $CD8^+$ T cell responses that blunt anti-tumor attack against azoxymethane/dextran sulfate sodium-induced colorectal cancers, resulting in higher tumor burdens[197] (Figure 2, immune evasion). These results are consistent with multiple clinical reports demonstrating that modulation of gut microbiota can promote responses to immune checkpoint blockade in solid cancers.[198,199] Greater memory $CD8^+$ T cell accumulation is detected in the lung of tobacco smokers, which could protect against tumor progression; however, it results in enhanced early selective pressure for tumors to develop immune escape via loss of antigen presenting machinery and neoantigens[200,201] (Figure 2, immune evasion). Taken together, these data establish that exogenous risk factors can either reduce immunosurveillance, enabling the outgrowth of tumors, or enhance tissue T cell activity, which in theory could limit tumor progression[165] but also drive premature T cell exhaustion and/or the emergence of immune evasive tumor cell clones.

TARGETING TUMOR PROMOTION: TOWARD MOLECULAR CANCER PREVENTION

Preventing the accumulation of oncogenic alterations may prove an insurmountable task, and, once acquired, are indelible from the genome. We have thus far detailed the ways in which these initiated cells are restrained from aberrant progression and the mechanisms by which cancer risk factors overcome such protective forces to prime for tumorigenesis. Our focus upon non-genetic tumor promotion is due to the inherent potential for reversibility and therefore future clinical applications (Figure 3). The primary focus of risk-factor induced cancer prevention should remain focused upon reducing exposure, including public awareness campaigns for safe sunlight exposure,[202] prevention of tobacco smoking in new users,[203] and legislation to limit asbestos use.[204] Yet some modifiable risk factors may prove more complex and are intertwined with systemic inequalities.[205] In addition to these primary prevention strategies, a nuanced understanding of the timing and duration of risk factor exposure, relative to individual susceptibility, will inform potential cancer screening protocols at the population level or within at-risk individuals, as well as understanding the intervention level necessary to prevent pre-invasive lesions from progression, both reviewed elsewhere.[206–209] Cancer-prevention studies by design require large cohorts of individuals to identify a sufficient number of cancer cases compared to controls, as well as long study periods to demonstrate reductions in either cancer incidence or mortality. These requirements alone make gathering convincing evidence extraordinarily difficult, and in order to pursue pharmaceutical intervention, there must be a large therapeutic window of a given agent and favorable risk-benefit ratio to justify such interventions. Strategies for molecular cancer prevention and clinical trial design are reviewed elsewhere[210]; here, we will discuss four current cancer prevention strategies through the lens of the molecular mechanisms by which they function, as well as speculation upon future interventions to reduce the onset of risk-factor-induced cancers.

Lifestyle change for cancer risk reduction

Obesity is associated with enhanced incidence of 13 different cancers, via cooperating inflammation, enabling tissue takeover, 3D tissue remodeling, enhancing progeny generation, generating susceptible cell lineages, and enabling immune evasion (Table 1). Evidence is emerging that obesity-associated cancers can be preventable, as weight loss reduces the incidence of many cancers in cohort and case control studies. In the Women's Health Initiative Observational Study, based in the USA, postmenopausal women with intentional weight loss had lower obesity-related cancer risk most strongly associated with protection from endometrial and colorectal cancers.[211] Weight loss in adulthood was associated with reduced risk of colorectal adenoma[212] and sustained weight change was also associated with lower risk of breast cancer in a cohort of postmenopausal women.[213] These studies demonstrate that tumor-priming inflammation and tissue reprogramming associated with obesity is potentially reversible, offering cancer prevention opportunities in the form of weight management or pharmacological intervention. Indeed, inflammatory markers, including IL-1 family members, are reduced in adipose and liver tissue of formerly obese patients after bypass surgery,[214] and a reduction in infiltrating macrophages in white adipose tissue has been observed[215] (Figure 3, lifestyle change). There is also evidence that weight-loss surgery results in reduction in circulating bile acids, in turn improving glucose tolerance and gut microbial communities through farsenoid-X receptor (FXR) signaling,[216] suggesting molecular drivers of obesity may be clinically targetable in addition to invasive surgical techniques. More research is needed not only upon the molecular mechanisms underpinning tumor initiation associated with obesity, but also to address if these pathways are maintained or mitigated upon weight loss[217] to potentially identify opportunities for intervention in at-risk individuals.

A better-studied example of "memory" of environmental exposures as related to future risk of tumor initiation is lung cancer formation in former smokers. Smoking cessation has been shown to reduce lung cancer incidence, where the cumulative risk of death from lung cancer by age 75 in male cigarette smokers is approximately 16%, compared to a risk of 10%, 6%, 3%, and 2% in former smokers who stopped at ages 60, 50, 40, and 30, respectively.[218] Indeed, there is evidence that in healthy airway epithelium in former smokers, basal stem cells harboring smoking-induced DNA damage are replaced by cells containing mutational burdens equivalent to never-smokers[59] (Figure 3, lifestyle change). Circulating inflammatory markers, such as C-reactive protein and white blood cell counts, decrease in ex-smokers within 5 years of quitting,[219] collectively suggesting that both the lung tumor-initiating and tumor-promoting role that smoking plays can be mitigated via a reduction of initiated cell pools and inflammatory microenvironments. Yet lung cancer risk still remains more than 3-fold higher in former heavy smokers

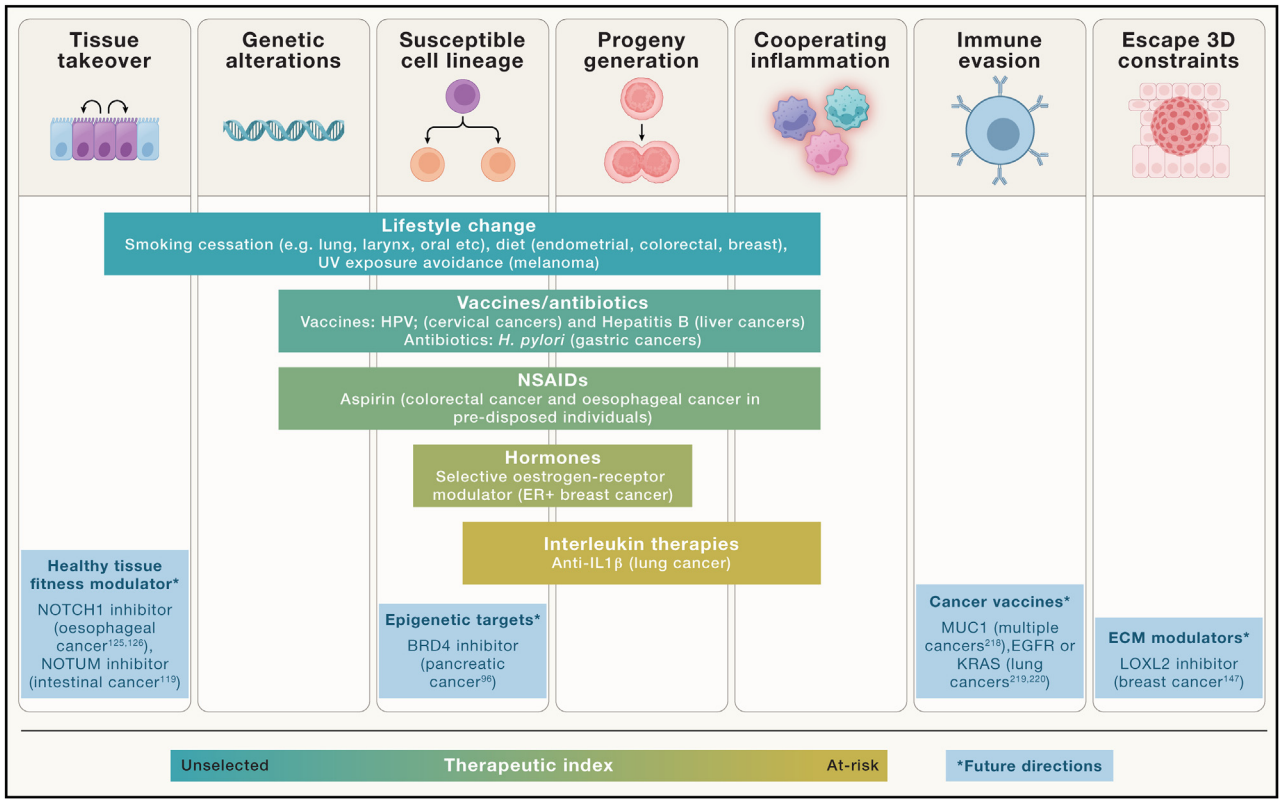

Figure 3. Molecular prevention leveraging the mechanisms of cancer risk factors

Cancer preventative strategies can target the mechanisms of tumor promotion. Each strategy is dependent on the therapeutic index for the intervention, balancing the risk-benefit ratio to either apply to the population level (blue) or at-risk individuals (yellow). Smoking cessation halts the further accumulation of genetic alterations and lowers inflammation and cell proliferation, potentially allowing cells with a lower mutational burden to gradually recolonize the tissue. Lifestyle changes are typically beneficial at the population level on unselected individuals. Tamoxifen hormone therapy reduces the risk of breast cancer by decreasing the pool of susceptible tumor-initiating cells and lowering their proliferation rate and is only recommended in at-risk individuals due to side effects beyond cancer prevention. Future clinical directions could target other hallmarks of tumor promotion, for example, the development of preventative cancer vaccines to promote immune surveillance for frequent clonal neoantigens associated with a given cancer or a pharmacological modulator of normal tissue fitness to drive the elimination of mutant cells. In all instances, identifying individuals who may benefit from intervention and defining treatment windows is necessary for successful preventative strategies.

compared to never-smokers, even more than two decades after quitting, and 40% of lung cancers in former smokers occur more than 15 years after quitting.[25] These data suggest a persistent memory of smoking-induced damage, or latent non-invasive lesions, in *some* ex-smokers that may be triggered to expand at a later time. Basal cell organoid forming efficiency is positively correlated with years of tobacco smoking and not with years since quitting,[220] suggesting a functional epithelial memory of smoking. In addition, promoter hypomethylation in circulating white blood cells is observed in former smokers 30–40 years post cessation,[221] indicating long-term alterations to hematopoietic stem cell pools in the bone marrow. This suggests some molecular changes extend beyond cessation of smoking and may offer opportunities for therapeutic intervention.

Vaccination and antibiotic intervention for cancer prevention

Primary prevention of infection-associated cancers includes suitable prophylactic vaccination programs, where HPV vaccinations have not only reduced the incidence of early neoplasias and cervical cancers,[222] but have been shown to induce regression of cervical intraepithelial neoplasias without surgical intervention[223] (Figure 3, vaccines). Neonatal hepatitis B vaccination programs begun in the 1980s have resulted in up to 80% reduction in the incidence of hepatocellular carcinoma.[224] Persons with active gastric ulcers or a history of ulcers can be tested for *H. pylori* infections and begin antibiotic treatments, which has resulted in a 40% reduction of gastric cancer incidence[225] (Figure 3, antibiotics). These interventions prevent inflammation, genomic alterations and altered epithelial cell differentiation that characterize tumor formation in these infection-driven cancers (Table 1).

Cancer vaccines can be used to provoke cellular or humoral adaptive immune memory of tumor-associated antigens to eradicate cancer cells (Figure 3, future directions). The approval of the first dendritic-cell-focused cancer vaccine for treatment of metastatic castration-resistant prostate cancer, sipuleucel-T, which targets the tumor associated antigen prostatic acid phosphatase, opens up the prospect to develop prophylactic vaccines for the prevention of non-viral cancers[226]; however, no

such preventative vaccine is currently approved. An effective cancer preventative vaccine would require identification of the appropriate candidate populations, a target antigen, an acceptable safety profile that does not induce intolerable autoimmunity, and an appropriate delivery strategy (reviewed in Finn[227] and Enokida et al.[228]). Currently, there are several anti-tumor vaccines in clinical development. The tumor-associated antigen MUC1, commonly overexpressed in diverse cancer types, has been targeted with an immunogenic peptide vaccine; administration of the vaccine resulted in long-lasting immune memory in 44% of individuals predisposed to colonic adenomas.[229] Pre-clinical mouse models of vaccines targeting overexpressed EGFR or KRAS in *EGFR*- or *KRAS*-mutant lung adenocarcinoma were protective against tumor formation[230,231] and could be deployed in selected populations at high risk of these cancers. Such vaccines could promote immune rejection or control of nascent tumors before the development of subclonal neoantigen diversity[232] (Figure 3, future directions).

Pharmacological intervention to reduce cancer risk

Interest in inflammation-driven cancers has led to the evaluation of cancer incidence as a secondary outcome in clinical trials of interleukin signaling inhibitors used to treat autoimmune diseases. Systematic review and meta-analyses from randomized trials of people treated with anti-TNF therapies for rheumatoid arthritis or inflammatory bowel diseases reported no significant increases in cancer incidence with treatment[233–236] nor within patients with rheumatoid arthritis treated with anti-IL-6 therapies[237] or within anti-IL-17A treated patients with psoriasis.[238] An intriguing secondary finding emerging from the randomized double-blind CANTOS trial investigating the effects of anti-IL-1β (canakinumab) in over 10,000 patients with a previous myocardial infarction[239] was a significant and dose-dependent reduction in incident lung cancers during a median follow-up period of 3.7 years[240] (Figure 3, interleukin therapies). New lung cancer diagnoses were significantly less frequent within the 150 mg and the 300 mg treatment group compared to the placebo arm, together with a reduction in recurrent cardiovascular events.[239,240] Canakinumab treatment was associated with dose-dependent reductions in C-reactive protein and IL-6 levels in circulating blood, yet did not affect circulating lipid levels, suggesting a broad reduction in systemic inflammation may prevent the onset of lung tumorigenesis, although replication of these data in formal cancer prevention setting are necessary. Yet the side effects of anti-IL-1β therapy includes increased susceptibility to fatal infection[239–241] and likely precludes it from use in molecular cancer prevention in an unselected population. Indeed, systemic antibody inhibition of pleiotropic cytokines will likely prove an ineffective cancer prevention strategy, due to eventual therapy resistance,[242] inability to provoke sufficient inflammation necessary to stimulate adaptive immune responses to nascent tumors,[243] and limiting essential tissue repair,[244] as well as serious adverse events.[241] A deep understanding of the intricate inflammatory networks that promote cancer formation is necessary in order to intervene and target key downstream regulators of tumor initiation in cancer predisposed individuals.

Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, have been used for their analgesic, antipyretic, and anti-inflammation effects for over a century and primarily work through inhibiting cyclooxygenase (COX) enzymes, ultimately reducing inflammatory signaling through decreasing prostaglandin levels. Aspirin was first reported in the 1950s to protect against myocardial infarctions,[245] and a 1980s observational study reported a reduced risk of colorectal cancer in aspirin users.[246] This led to a plethora of randomized controlled trials due to the favorable safety profile of aspirin and the potential simultaneous protection from cardiovascular disease. Long-term, low-dose aspirin use was initially demonstrated to reduce risk of colorectal cancer incidence in unselected adult (>50 years old) populations,[247,248] yet serious side effects were reported, most notably gastrointestinal bleeding (reviewed in Cuzick et al.[249]). It is unclear if long-term aspirin use reduces colorectal cancer incidence to justify the risk-benefit profile and is not currently recommended for cancer prevention in healthy individuals.[250] Yet in patients predisposed to colorectal cancer development, including those with Lynch syndrome, taking daily aspirin for at least 2 years is recommended to reduce colorectal cancer incidence, and in patients with familial adenomatous polyposis, aspirin use could delay the need for colectomy for the near 100% penetrance of colorectal cancers in this at-risk group[251,252] (Figure 3, NSAIDs). WNT-Beta-catenin signaling is a key regulator of healthy colorectal stem cells, and almost all colorectal cancers demonstrate WNT pathway hyperactivation.[253] Aspirin likely functions through the inhibition of prostaglandin synthesis, resulting in reduced levels of PGE2, a key driver of WNT signaling through the EP2 receptor.[254,255] There is also evidence that aspirin can reduce beta-catenin levels through inhibition of protein phosphatase 2A, resulting in greater levels of beta-catenin ubiquitylation and degradation.[255] An emerging use of aspirin is in Barrett's esophagus patients where a small prospective trial revealed that NSAID users, particularly those with enhanced genetic abnormalities in preneoplastic tissue, had a reduced risk of progression to esophageal adenocarcinoma compared to that of non-users[256] (Figure 3, NSAIDs). This observation has since been confirmed in a larger randomized trial where aspirin was used in combination with proton pump inhibitors.[257] The mechanism of tumor progression may be different from that suggested in colorectal cancer, given that esophageal adenocarcinoma is not a WNT-driven disease and is characterized by high levels of genomic instability and *TP53* mutations.[258,259] One report noted that NSAID use slowed the rate of somatic genomic evolution in Barrett's esophagus, reducing the acquisition of new genomic alterations.[260] This is supported by an earlier study in 350 people with Barrett's esophagus reporting a 56% reduction in tetraploid and 75% reduction in aneuploid lesions in current NSAID users.[261] The use of NSAIDs in patients with higher risk of colorectal or esophageal cancers is a key example of molecular cancer prevention (Figure 3, NSAIDs), where defined dosage levels and periods of use, integrated with screening,intervention, and communication of risk-benefit ratios with informed patient choice should guide future prevention programs.

Epidemiological and experimental evidence suggested that estrogen promotes the formation of breast cancer. Successful treatment of patients with hormone receptor-positive breast

cancer with tamoxifen, a selective estrogen-receptor modulator (SERM) with little side effects, led to the proposal of tamoxifen use for the prevention of breast cancer.[262] Tamoxifen or other SERMs are now recommended for patients at a high risk for breast cancer, either from familial history (excluding BRCA1 patients) or previous treatment for ductal carcinoma *in situ*, and at a low risk of adverse reactions, including osteoporosis, blood clotting, and endometrial cancer (Figure 3, hormones). Tamoxifen or other SERMs have been shown to reduce the incidence and mortality of breast cancer.[263] Tamoxifen exerts its anti-tumor effects by limiting estrogen-dependent breast epithelial cell proliferation, which occurs primarily in the early phase of the menstrual cycle[264,265] and can also affect hormone receptor-negative mammary stem cells through paracrine signaling.[266] This likely results in reduced accumulation of genetic errors leading to breast carcinogenesis.[267,268] Tamoxifen treatment is only recommended for 5 years of use but offers protection up to 8 years after cessation,[263] suggesting persistent adaptation within the breast-to-estrogen signaling blockade. Altogether, these are examples of where understanding the biological mechanism of cancer promotion and identification of high risk individuals has aided the development of targeted therapeutics, which reduce cancer formation.

Future perspectives on molecular cancer prevention

It is unlikely that we can prevent the development of somatically acquired genomic alterations, generated due to environmental carcinogens or intrinsic mechanisms, that contribute to cancer initiation; these alterations are irreversible once formed. A deep knowledge of the biological mechanisms involved in restraining tumor initiation in homeostasis and the promoting forces reviewed here will identify pathways that may be reversible (Figure 3). Identification of the cancer cell(s) of origin is a critical step toward this goal; this will allow for earlier detection of malignancies, better prediction of tumor behavior, and potential development of preventative therapies targeting the unique properties of the tumor-initiating cell. With the growing body of evidence suggesting epigenetic states as a regulator of lineage susceptibility, a deep understanding of oncogenic competence related to epigenomic states within each cell lineage could have relevance across diverse patient backgrounds, especially when combined with germline risk, for the prediction of tumor initiation after specific oncogenic insults and appropriate therapeutic interventions. Epithelial tissues are dynamic, competitive environments with pre-clinical evidence suggesting that pharmacological intervention can increase wild-type cell fitness to outcompete and eliminate mutant cells. Early T cell surveillance may prevent cancer formation and strategies to boost anti-cancer immunity, via cancer vaccines or augmentation of TCR signaling, could comprise new strategies for cancer prevention. Broad anti-inflammatory strategies have so far proved successful in preventing colorectal and esophageal cancer progression with acceptable toxicity profiles. Better defined inflammatory pathways within each tissue type and their downstream effectors (often tumor-initiating cells) may reveal new strategies for the prevention of inflammation-associated cancers. Intervention strategies will also limit multiple promotion mechanisms, and understanding the required timing for each step is an important future direction (Figure 3). Improved delivery mechanisms of anti-inflammatory treatments for localized inflammation could overcome unwanted systemic effects. Chemoprevention strategies work when offered to at-risk individuals, for a defined period of time at appropriate dosage, with judicious monitoring of toxicities. Defining at-risk populations is crucial for appropriately powered clinical trials, to enhance the acceptable risk-benefit ratio, and minimize undue harm. By elucidating the causes of tumor promotion across tissues that act upon latent clones harboring oncogenic alterations, the development of new molecular cancer preventative strategies may be a reality.

ACKNOWLEDGMENTS

C.E.W. is supported by a RESPIRE4 fellowship from the European Respiratory Society and Marie Sklodowska-Curie Actions. W.H. is funded by a European Research Council Advanced Grant (PROTEUS, grant agreement no. 835297), Cancer Research UK Early Detection and Diagnosis Primer Award (EDDPMA-Nov21\100034), The Mark Foundation (grant 21-029-ASP), and has been supported by Rosetrees. E.L.L. receives funding from Novo Nordisk Foundation (ID 16584), The Mark Foundation (grant 21-029-ASP), and has been supported by Rosetrees. E.G. is supported by a European Research Council Advanced Grant (PROTEUS, grant agreement no. 835297) under the European Union's Horizon 2020 research and innovation program. C.S. is a Royal Society Napier Research Professor (RSRP\R\210001). His work is supported by the Francis Crick Institute that receives its core funding from Cancer Research UK (CC2041), the UK Medical Research Council (CC2041), and the Wellcome Trust (CC2041). C.S. is funded by Cancer Research UK (TRACERx [C11496/A17786], PEACE [C416/A21999], and CRUK Cancer Immunotherapy Catalyst Network); Cancer Research UK Lung Cancer Center of Excellence (C11496/A30025); the Rosetrees Trust, Butterfield and Stoneygate Trusts; Novo Nordisk Foundation (ID16584); Royal Society Professorship Enhancement Award (RP/EA/180007); National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Center; the Cancer Research UK-University College London Center; Experimental Cancer Medicine Center; the Breast Cancer Research Foundation (US) (BCRF-22-157); Cancer Research UK Early Detection and Diagnosis Primer Award (grant EDDPMA-Nov21/100034); and The Mark Foundation for Cancer Research Aspire Award (grant 21-029-ASP). This work was supported by a Stand Up To Cancer-LUNGevity-American Lung Association Lung Cancer Interception Dream Team Translational Research Grant (grant no.: SU2C-AACR-DT23-17 to S.M. Dubinett and A.E. Spira). Stand Up To Cancer is a division of the Entertainment Industry Foundation. Research grants are administered by the American Association for Cancer Research, the Scientific Partner of SU2C. C.S. is in receipt of an ERC Advanced Grant (PROTEUS) from the European Research Council under the European Union's Horizon 2020 research and innovation program (grant agreement no. 835297).

DECLARATION OF INTERESTS

C.S. acknowledges grant support from AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Pfizer, Roche-Ventana, Invitae (previously Archer Dx Inc - collaboration in minimal residual disease sequencing technologies), Ono Pharmaceutical, and Personalis. He is an AstraZeneca Advisory Board member and Chief Investigator for the AZ MeRmaiD 1 and 2 clinical trials and is also Co-Chief Investigator of the NHS Galleri trial funded by GRAIL and a paid member of GRAIL's Scientific Advisory Board. He receives consultant fees from Achilles Therapeutics (also a SAB member), Bicycle Therapeutics (also a SAB member), Genentech, Medicxi, China Innovation Center of Roche (CICoR) formerly Roche Innovation Center – Shanghai, Metabomed (until July 2022), and the Sarah Cannon Research Institute. C.S. has received honoraria from Amgen, AstraZeneca, Pfizer, Novartis, GlaxoSmithKline, MSD, Bristol Myers Squibb, Illumina, and Roche-Ventana. C.S. had stock options in Apogen Biotechnologies and GRAIL until June 2021, and currently has stock

options in Epic Bioscience, Bicycle Therapeutics, and has stock options and is co-founder of Achilles Therapeutics. C.S. is an inventor on a European patent application relating to assay technology to detect tumor recurrence (PCT/GB2017/053289), the patent has been licensed to commercial entities, and under his terms of employment, C.S. is due a revenue share of any revenue generated from such license(s). C.S. holds patents relating to targeting neoantigens (PCT/EP2016/059401), identifying patient response to immune checkpoint blockade (PCT/EP2016/071471), determining HLA LOH (PCT/GB2018/052004), predicting survival rates of patients with cancer (PCT/GB2020/050221), identifying patients who respond to cancer treatment (PCT/GB2018/051912), a US patent relating to detecting tumor mutations (PCT/US2017/28013), methods for lung cancer detection (US20190106751A1) and both a European and US patent related to identifying insertion/deletion mutation targets (PCT/GB2018/051892), and is co-inventor to a patent application to determine methods and systems for tumor monitoring (PCT/EP2022/077987).

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