REVIEW ARTICLE

Consensus report of the 8 and 9th Weinman Symposia on Gene x Environment Interaction in carcinogenesis: novel opportunities for precision medicine

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Abstract

The relative contribution of intrinsic genetic factors and extrinsic environmental ones to cancer aetiology and natural history is a lengthy and debated issue. Gene–environment interactions (G x E) arise when the combined presence of both a germline genetic variant and a known environmental factor modulates the risk of disease more than either one alone. A panel of experts discussed our current understanding of cancer aetiology, known examples of G × E interactions in cancer, and the expanded concept of G × E interactions to include somatic cancer mutations and iatrogenic environmental factors such as anti-cancer treatment. Specific genetic polymorphisms and genetic mutations increase susceptibility to certain carcinogens and may be targeted in the near future for prevention and treatment of cancer patients with novel molecularly based therapies. There was general consensus that a better understanding of the complexity and numerosity of G × E interactions, supported by adequate technological, epidemiological, modelling and statistical resources, will further promote our understanding of cancer and lead to novel preventive and therapeutic approaches.

Facts

- Gene–environment interaction indicates that combination of a genetic and an environmental factor modulates the risk of cancer more than either one alone.
- Lifetime risk of cancers of many different types was shown to strongly correlate with the total number of divisions of the normal self-renewing stem cells.
- Specific genetic polymorphisms and mutations increase susceptibility to certain carcinogens.
- p53 is a prototype genetic factor for cancer, it can be somatically or inheritably mutated, as well as subjected to polymorphism.

- All carriers of inherited BAP1 mutations have developed one or more cancers during their lifetime. Exposure to asbestos and UV-light further increases their risk of developing mesothelioma, melanoma and skin cancers: GXE interaction.

Questions

- Why environmental carcinogens cause cancer only in a fraction of exposed individuals?
- Alterations in *TP53* and *BAP1* genes both predispose to cancer, but with a different spectrum. What are the underlining molecular determinants of this specificity?
- Will single cell analysis resolve the difficulties in diagnosis and study associated to tumour heterogeneity?
- Can we design prophylactic or therapeutic anti-cancer approaches based on genetic of polymorphisms and mutations?

The origin of cancer: studies clash over 'intrinsic' versus 'extrinsic' risk

Hypotheses on the origin of cancer are integral part of the history of medicine. The first three evidences supporting the presence of extrinsic chemical risk factors date back to the XVIII century: John Hill's record on tobacco snuff and nasal cancer; Percivall Pott's association between exposure to soot and scrotal cancer; Samuel von Sömmerring's observation of a relationship between lip carcinoma and clay-pipe smoking [1]. Recognition of the existence of intrinsic genetic risk factors is more recent, and originated from analyses of familial clustering of cancer cases and is experimentally supported by numerous efforts to generate murine models of hereditary cancers [2]. Epidemiological studies have demonstrated that environmental carcinogens cause cancer only in a fraction of exposed individuals; the biological reasons are often unknown.

Taking advantage of the extremely large amount of data generated in the last 20 years, bioinformatics represents a powerful tool to investigate both the interactions between genes and environment in determining cancer risk and the origin of cancer itself. In the last few years, a great interest has been raised on this topic by a series of articles. Tomasetti & Vogelstein's in 2015 reported that lifetime risk of cancers of many different types is strongly correlated with the total number of divisions of the normal self-renewing stem cells maintaining tissues' homoeostasis [3], thus supporting a prevalent 'bad-luck' intrinsic origin of cancer. Wu et al. instead proposed that the overwhelming majority of cancers develop following exogenous damage, with only ~ 10–30% of the risk attributable to intrinsic factors, thus supporting the 'toxic insults' theory [4]. These studies provide correlations, without entering into causal molecular mechanisms, but the message of these papers could not be in more strident contradiction, with the effect of igniting a public debate on this very hot topic.

Unique occurrences of cancer epidemics in remote regions of the world have provided definitive proof for the gene X environment hypothesis. In particular, studies of an epidemic of mesothelioma in Cappadocia, Turkey, where over 50% of the population exposed to carcinogenic erionite fibers dies of mesothelioma, the most devastating cancer epidemic ever recorded in medicine, revealed that susceptibility to mesothelioma was transmitted in a Mendelian fashion and that the cause of the epidemic was gene–environment interaction [5–7].

Expanding the concept of gene–environment interaction (G × E)

In the complex picture of cancer pathogenesis and progression, it is now clear that both external environmental and genetic factors affect the so-called microenvironment, i.e. the local cellular milieu where cancer develops, which has a critical role in determining cell fate (Fig. 1).

Gene–environment interactions arise when the combined presence of both a genetic and an environmental factor modulates the risk of cancer more than either one alone. The traditional definition of G × E interaction most often implies 'intrinsic' genetic mutations (i.e. polymorphisms and rare germline mutations) and 'non-iatrogenic' environmental factors. Moreover, in cancer patients two additional levels of complexity arise: 'acquired' genetic mutations and 'acquired iatrogenic' environmental factors (e.g. drugs, radiotherapy) contribute to the cancer phenotype (Figs 2 and 3). Understanding the mutual relationships between all these factors is crucial both from a scientific and from a clinical perspective.

The International Weinman Conferences, held at the University of Hawaii Cancer Center, Honolulu, HI, in 2017 (January 26, 27 and November 30–December 1) were conceived to stimulate discussions among experts from different fields of cancer research on complex inter-relations between genetics, external environment and microenvironment relevant to cancer aetiology—thus trying to find common ground in the lengthy conflict between 'bad-luck'

Fig. 1 Gene–environment and cancer pathogenesis. Both genetics and environment interact to affect the microenvironment from which ultimately causes cancer to develop in the first place and then progress
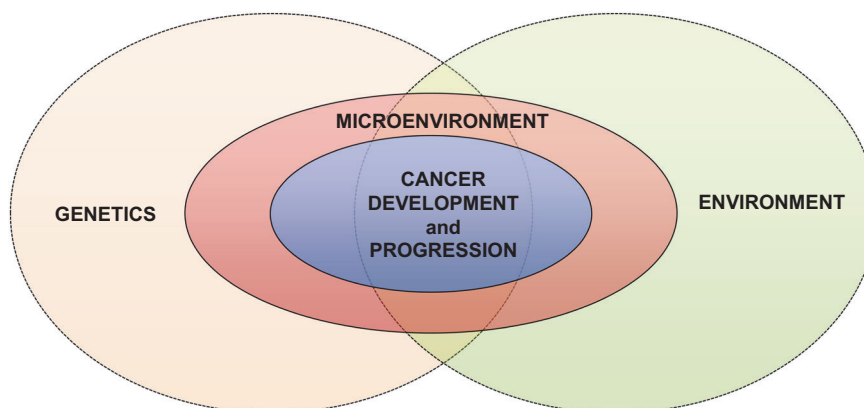
Fig. 2 The complexity of gene–environment interactions. Including somatic cancer mutations and anti-cancer treatments further increases the layers of gene–environment interactions, providing us with the opportunity to increase our understand the of complexity of the cancer phenomenon
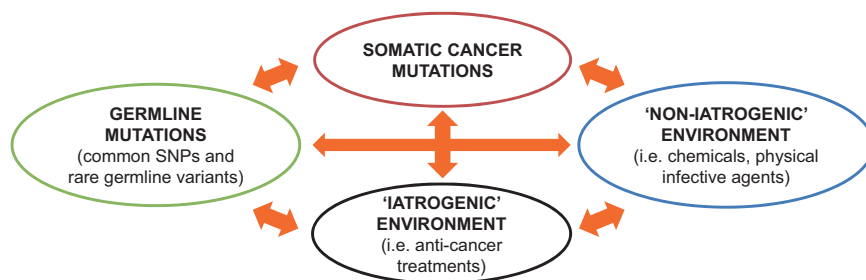
Fig. 3 Environmental pressure and cancer susceptibility. A number of extrinsic factors associated to lifestyle, early-life influence or pre-existing chronic conditions exerts pressure on cancer insurgence. The genetic background, including somatic mutations, germline mutations and single nucleotide polymorphism contributes to the outcome of the impact of these environmental factors on the organism. Some extrinsic factors can also promote alteration of the genetic information producing mutagenic events that trigger cancer
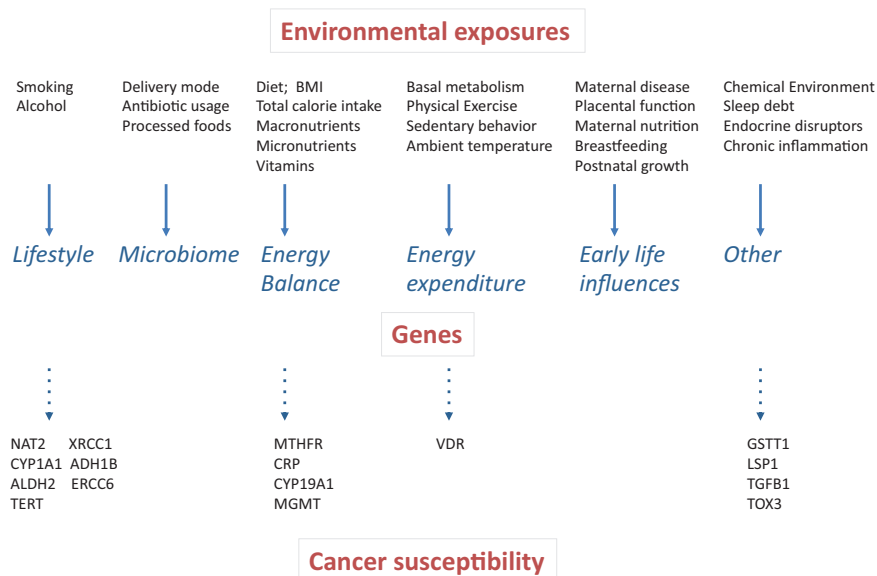
and 'toxic insults', and to cancer progression and therapy. Here, we describe exemplificative topics on G × E interactions in both solid and haematologic malignancies presented by the authors, and the conclusions they reached following the discussions.

Genome-wide association studies, environment and molecular biology

Despite the unclear contribution of each single factor, it is commonly accepted that the risk of developing cancer is determined by a complex interplay of both genetic and environmental factors [8–10]. There are many well-established environmental and lifestyle risk factors for various cancers, including smoking, alcohol, ionizing and solar radiations, exposure to carcinogenic fibres present in the environment, such as asbestos and erionite, as well as occupational exposures to these same fibres, infectious agents, obesity, and physical inactivity, which together are thought to account for up to 60% of cancer deaths in the United States [11]. However, only a small fraction of individuals exposed to these risk factors develop cancer, suggesting the co-existence of intrinsic genetic susceptibility.

Recent genome-wide association studies (GWAS) and next-generation sequencing studies have identified many common and rare germline genetic variations that contribute to increased cancer risks. Many of these cancer susceptibility loci are located in or near genes involved in DNA repair, or epigenetic regulators of gene transcription; however several examples exist of variants in genes involved in carcinogen metabolism. A paradigmatic example is the interaction between N-acetyltransferase 2 (NAT2) gene polymorphisms and smoking in elevating bladder cancer risk. NAT2 is a phase II detoxification enzyme that catalyses the metabolic inactivation of aromatic amines and heterocyclic amines, constituents of cigarette smoking and other environmental exposure. NAT2 polymorphisms allow classification of the human population into rapid, intermediate and slow 'acetylator' phenotypes. Numerous population studies and a meta-analysis [12] confirmed that NAT2 slow acetylators, resulting in slow detoxification of tobacco carcinogens, have a 1.4-fold increased risk of bladder cancer, and identified a significant synergistic interaction between NAT2 genotype and smoking: individuals with the NAT2 slow acetylating genotype who are also heavy smokers exhibited the highest risk of developing bladder cancer [12]. Another eminent example is

represented by the interaction between aldehyde dehydrogenase (ALDH2) gene variants, alcohol metabolism and oesophageal cancer [13].

Based on these and other data, there is a clear need for so-called 'gene–environment-wide association studies' which take into account environmental factors together with genetic variations to explain complex traits and phenomena [14]. Moreover, while in selected cases such as those represented by NAT2 and ALDH2, it is possible to infer the mechanistic link between the genetic variants and the consequent molecular alterations, a further step is needed to improve our understanding of G × E interactions from a molecular perspective, as shown by recent efforts in this direction [15].

Taking advantage of unique epidemiological resource

The study of G × E interaction requires the capability of discerning as much as possible the contribution of each of the two elements to the observed phenotype. Compared to small families and close relatives, which often share environment and lifestyle besides genes, such interactions can be more clearly elucidated studying distant relatives and high-risk pedigrees.

A unique resource that combines extensive genealogy with cancer and exposure data, the Utah Population Data Base (UPDB), provides the opportunity to better understand the contribution of genes, of the environment, and their combined effects to cancer. The UPDB represents the genealogy of the Utah Mormon pioneers and their descendants. The original Utah genealogy included 1.6 million individuals linked in genealogies 6–7 generations deep [16], and has been expanded from the 1970s with relationship data from Utah Vital Statistics records. State-wide SEER cancer data since 1966 for over 300,000 individuals have been linked to this database. The UPDB today represents 7 million Utah residents, of which 3 million have 3–16 generations of data. The power of the UPDB for G × E interaction studies lies in the simultaneous record of exposure data (such as tobacco use or radon exposure, both available in the UPDB), data for cancer incidence, and data on genetic relationships.

Health-related predisposition genes can be identified, and G × E interactions can be elucidated in high-risk pedigrees using these powerful genealogical resources. Analysis of UPDB high-risk pedigrees identified BRCA1, BRCA2, and CDKN2A as cancer predisposition genes [17–19], and studies of environmental exposures in individuals sharing genetic predisposition variants have clarified G × E interactions in cancer [20–22].

Similar efforts in creating large databases including both environmental and genetics data are steadily increasing in number, as they provide invaluable opportunities to study the complexity of cancer. Among the most recent examples, are the Iceland cohort [23], the Swedish Family-Cancer Database [24], and the US Veterans Genealogy Project [25].

The case of malignant mesothelioma and BAP1

Malignant mesothelioma (MM) is often used as the "standard" example of a cancer caused by G × E interaction. Epidemiologically, MM is an aggressive polyclonal cancer [26] associated with occupational and/or environmental exposure to tumorigenic mineral fibres, such as asbestos, erionite, or other non-regulated asbestos-like fibres [27–30]. However, "only" ~ 5% of asbestos workers exposed to asbestos continuously for over 10 years developed MM, suggesting that monogenic or polygenic genetic predisposition also contributes to MM risk [27]. Therefore, inherited genetic variants in genes encoding for proteins involved in the DNA damage response and/or in the inflammatory response may likely modulate the risk of asbestos-induced MM. Once they reach the mesothelium, asbestos fibres cause mesothelial cell death and chronic inflammation, associated with the release of damage-associated molecular patterns (DAMPs) molecules and cytokines [27]. Among these DAMPs, the active and passive release of different isoforms of high-mobility group box 1 (HMGB1) protein [31] sustains the chronic inflammatory response, with secretion of TNF-α and reactive oxygen species (ROS) [32, 33] (Fig. 4). Moreover, asbestos fibres can also directly induce ROS production because of the iron they contain, which behaves as a catalyst for free-radical generation [34, 35]. These molecules in turn activate NF-κB, leading to the survival of mesothelial cells that have accumulated genetic damage [32]. Accordingly, anti-inflammatory drugs and HMGB1 inhibitors impair MM growth in vitro and in experimental animal models and could represent prophylactic and therapeutic approaches [36–38].

BRCA1-associated protein 1, BAP1 is the most frequently mutated gene in MM, as about 2/3 of sporadic cases—i.e., MM not developing in carriers of germline BAP1 mutations—carry somatic BAP1 mutations [39, 40]. Besides single nucleotide variations and other intragenic alterations, frequently MM have large copy number variations and micro-deletions reminiscent of chromothripsis. Most common are minute deletions (ranging between 100 bp and 3000 bp) in chromosome band 3p21 in genes encoding for epigenetic modifiers such as BAP1 and others, e.g. SETD2, SCAP, SMARCC1, PBRM1 [39]. Because BAP1 mutations are very rare in lung cancer, the presence or absence of wild-type BAP1, easily detected as
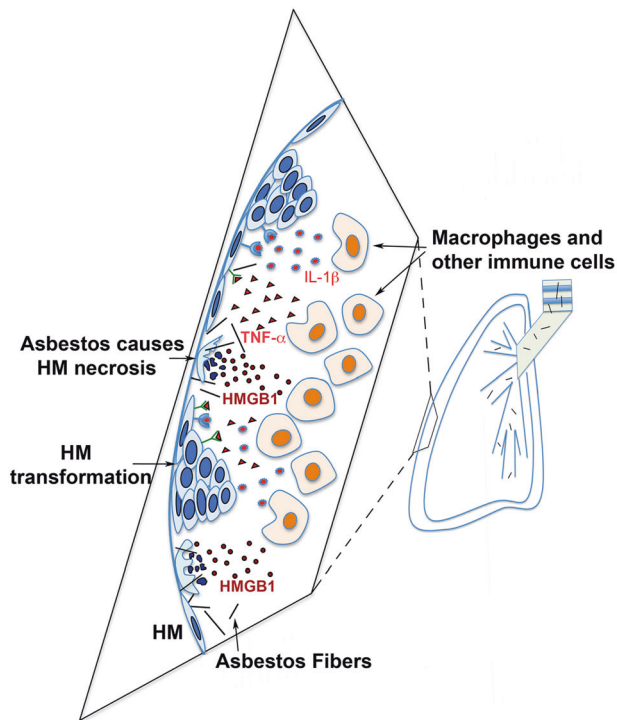
Fig. 4 Asbestos pathogenesis leads to mesothelioma. Asbestos fibers travel to pleura and cause human mesothelial cells (HM) to die of necrosis, leading to the release of HMGB1 into the extracellular space. HMGB1 induces macrophages and other inflammatory cells to accumulate and triggers the inflammatory response and leads to the secretion of cytokines such as TNF-α and IL-1β, which stimulate survival signalling pathways that increase survival of asbestos-damaged HM. This allows key genetic alterations to accumulate within HM that sustain asbestos-induced DNA damage that over time may lead to HM transformation and mesothelioma development

presence or absence of nuclear BAP1 immunostaining helps pathologists differentiate MM from lung cancer [41]. A better characterization of the most common molecular modifications in MM should pave the way to novel and more specific therapies [42].

In this respect, germline BAP1 mutations significantly increase the risk of MM, even among individuals not exposed to asbestos [43, 44]. Intriguingly, patients with MM who also carry germline BAP1 mutations have prolonged survival [45].

How to reconcile the environmental and the genetic factor in MM pathogenesis? The incidence of germline BAP1 mutations is low among sporadic MM patients, suggesting that other yet unknown genetic mutations might contribute to MM risk [46]. Based on the experimental evidence in mice, germline BAP1 mutations significantly increase the risk of asbestos-induced MM after exposure to low levels of asbestos, levels that rarely cause MM in wild-type mice [47, 48]. Germline BAP1 mutations are not only associated with MM, but also with a wider recently

identified cancer predisposition syndrome which includes cutaneous and uveal melanoma, squamous and basal cell carcinoma (all associated to sunlight exposure) as well as to clear cell renal cell carcinoma (ccRCC) a malignancy not yet associated with a specific carcinogen. Moreover, although less frequent, carriers of germline BAP1 mutations develop also several other malignancies, such as breast cancer, cholangiocarcinoma, sarcomas, brain tumors, etc., suggesting that BAP1 mutations increase the overall cancer risk although those associated to environmental carcinogens predominate [49].

The case of clear cell renal cell carcinoma and *BAP1*

BAP1 is commonly mutated at the somatic level in ccRCC, and is one of two genes that underlie the first molecular genetic classification of ccRCC [50]. Mutations in BAP1 (found in ~15% of ccRCC) tend to anti-correlate with mutations in *PBRM1* (found in ~50% of ccRCC). Both *BAP1* and *PBRM1* are two-hit tumour suppressor genes and they reside on chromosome 3p. Chromosome 3p harbours the VHL tumour suppressor gene, which is mutated (or silenced) in the majority of ccRCC. *VHL* mutation is an initiating event and this mutation is followed by loss of 3p, which eliminates the second copy of *VHL* as well as one copy of *BAP1* and *PBRM1* [51]. In mice, inactivation of *VHL* is insufficient for tumour development, but RCC develops if *VHL* and either *BAP1* or *PBRM1* are targeted [52]. In humans, PBRM1-deficient tumours tend to be of low grade and BAP1-deficient tumours are typically of high grade (and associated with poor survival), and this is reproduced in mice [52]. These findings provide insight into the mechanism of renal cancer development and pave the way for tailored treatment approaches.

Besides *BAP1* [53] renal cancers can be associated with germline mutations in a variety of genes, such as *VHL*, FH and genes encoding for the different subunits of the succinate dehydrogenase [54]. It is also notable, that some families with *BAP1* germline mutations appear to be almost exclusively affected by renal cancer [53, 55]. However, compared to other cancer types, the interactions between genetic and environmental factors in the pathogenesis of renal cancer is less understood. Recent studies have proposed G × E interactions in the aetiology of renal cancer between specific loci and consumption of cooked meat, which translates into higher intake of dietary mutagenic polycyclic aromatic hydrocarbons/heterocyclic amines [56]. Understanding the interplay between these environmental factors and germline mutations predisposing to renal cancer is an expanding area of research [57].

p53 family members in cancer predisposition and development: between macro- and micro-environment

The most well studied tumour suppressor in cancer development is *TP53*, which encodes the tumour suppressor protein p53 [58–64]. Mutations in the p53 effector pathway significantly influence the relative incidence of tumour development and progression [65–67]. Indeed, *p53* is the most frequently mutated protein among all human cancers, being mutated in over 50% of cancers [68, 69]. Notably, TP53 mutations and polymorphisms are often associated with the emergence of oncogenic "gain–of–function" activities by the protein product, which further contribute to cancer development. For example, the expression of mutant forms of p53 (missense mutations) affects cellular motility and invasion through several pathways, often involving the other members of the p53 family [70–75]. These evidences are derived from both somatic mutations and rare inherited mutations occurring in the Li-Fraumeni cancer syndrome [66].

Moreover, recent bioinformatics analyses of whole genome data showed that frequent germinal isoforms of the TP53 gene have a profound effect on the relative incidence of many cancers.

Also distinct single nucleotide polymorphisms (SNPs) of TP53 are strongly associated with cancer development, making the entire p53-pathway very relevant to cancer development [76]. TP53 mutations are a potent 'intrinsic' driver of cancer development. However, TP53 variants have also emerged in G × E interactions studies. For example, TP53 polymorphisms appear to modulate human papillomavirus (HPV)-induced cancer risk, through differential targeting of the p53 variant proteins by the E6 viral oncoprotein [77].

The p53 family, which includes p53, p63 and p73, exerts a number of critical biological functions, such as regulating cellular processes critical for development, homeostasis and more importantly tumour suppression. Some of these functions are shared by all members of the p53 family, others are exclusive functions of specific members [78–80]. The canonical pathway for activation of p53 family members follows the DNA damage insults. However, a revised model for p53 family suggests that several types of insults, such as hypoxia, nutrient fluctuation, oxygen radicals, etc., lead to activation of these proteins and regulation of a wide range of biological processes [81]. This makes the p53 family particularly relevant in interaction with the environment. For example, G × E interactions have been proposed between TP73 polymorphisms and smoking and obesity in modifying lung cancer risk [82].

The molecular connections between specific genetic variants and functional consequences are still unclear. We know that, similarly to the best-characterised member p53, both p73 and p63 are transcribed as two distinct isoforms TA-isoforms and ΔN-isoforms, containing, or not, the N-terminal transactivation domain [81]. Both p63 and p73 are involved in female infertility maternal reproduction [83] and in cancer development and progression. For example, ΔNp63 might control cancer development through regulation of Sonic Hedgehog signalling [84] and regulation of the metabolism via Hexokinase II [85]. Conversely, in vivo experiments have shown a tumour suppressor role for TAp73 and an oncogenic role for ΔNp73, whose deletion is associated with neurological phenotype [86, 87]. Moreover, recently, the transcription factor TAp73 has been demonstrated to oppose hypoxia-induced factor (HIF)-1 activity promoting its polyubiquitination and consequent proteasomal degradation, and thus affecting tumour angiogenesis [81, 88].

It is still unclear whether additional genetic polymorphisms and/or environmental factors might modulate the ratio of transcribed mRNA and/or transduced protein of the different isoforms of the p53 family. A deeper understanding of these processes will be beneficial for preventing negative outcome in the interaction between genes and environment and for improving pharmaceutical intervention for cancer and toxicity-associated disease.

The p53 family also regulates the interaction between cells and their microenvironment through regulation of cellular metabolism, promoting oxidative metabolism, glutaminolysis and serine biosynthesis, thus promoting GSH production to buffer oxidative stress [89–95]. The key function that the p53 family exerts in control of redox status represents a pivotal contribution to interaction with environmental stressors and this can be expanded beyond the tumour protective role of this family of genes [96]. The influence of p73 and p53 on serine biosynthesis and one-carbon metabolism not only represents a barrier against tumour transformation, but could also influence the response of cancer cells to anti-metabolic drugs that target enzymatic activities of these pathways [97–99].

An additional layer of complexity in the interaction of p53 family with the microenvironment is added by the recent discovery of an influence of p53 on the mevalonate pathway. The mevalonate pathway has been implicated in multiple aspects of tumour biology, including growth, proliferation, recurrence and metastasis [100]. Mutant p53 can upregulate expression of mevalonate pathway genes, possibly through interaction with SREBP-2, the key transcriptional factor of many sterol biosynthesis genes, and this determines a susceptibility of the mevalonic pathway to the p53 status in the cancer cells [74]. One of the important outputs of the mevalonate pathway is RhoA geranylgeranylation which can lead to stabilized mutant p53 [101]. Interestingly, statins also destabilize mutant p53, although

the mechanism appears to involve counteracting DNAJA1 interaction with mutant p53 [102]. Statins target the activity of the HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway. These compounds, widely used for treatment of hypercholesterolemia, have been reported to be protective for certain cancers [103, 104]. Pre-clinical studies indicate that targeting mevalonic pathway, alone or in combination, may offer designed therapeutic options for patients bearing p53 mutant tumours.

A full characterisation of the interaction between genetic landscape and response to treatment targeting metabolic pathways would be desirable to improve therapeutic efficacy in cancer patients.

Regulation of IP$_3$ receptors through oncogenes and tumor suppressors

IP$_3$ receptors (IP$_3$Rs) are IP$_3$-activated Ca^{2+} release channels located on intracellular Ca^{2+} stores mainly at the endoplasmic reticulum (ER), and play critical roles in the regulation of the Ca^{2+} release from the store [105–107]. Recently IP$_3$Rs have been found to have pivotal roles in the regulation of cell death and survival by controlling Ca^{2+} transfer from ER to mitochondria. There are three isoforms in human and rodents, IP$_3$R1, IP$_3$R2 and IP$_3$R3, with different tissue distributions and different IP$_3$ binding affinity [108–113]. IP$_3$Rs are huge tetrameric channels with each monomer composed of about 2700 amino acids. IP$_3$Rs bind several proteins that influence IP$_3$Rs activities. IP$_3$Rs are divided into five domains: The N-terminal suppressor domain, the IP$_3$ binding domain, the regulatory/coupling domain, the channel domain with six transmembrane regions, and the C-terminal gatekeeper domain IRBIT pseudo ligand of IP$_3$ binds to the IP$_3$-binding core. The C-terminal gatekeeper domain is targeted by various regulatory proteins including Bcl-2, Bcl-X$_L$, Mcl-1, cytochrome c, K-Ras4B, Akt, Huntingtin, BRCA1, GIT, protein and 4.1 N and 80K-H [114–123].

The tumor suppressors PTEN and BAP1 regulate IP$_3$R stability and intracellular Ca^{2+} dynamics, and increase apoptosis sensitivity of cancer cells [124, 125]. X-ray crystallographic and mutagenesis analyses, together with functional analyses, have revealed a leaflet structure in the large regulatory cytosolic domain that is critical in transmitting the IP$_3$-dependent global conformational change to the channel domain [126].

IP$_3$Rs at ER-mitochondria contact sites

The localization of IP$_3$Rs in specialized microdomain of ER called mitochondria-associated ER membranes (MAMs) is critical in the regulation of cell death and survival. Mitochondrial Ca^{2+} uptake systems needs close proximity to high Ca^{2+} microdomains of IP$_3$R-mediated Ca^{2+} release sites [127–129]. MAMs are the physical contact site between ER and mitochondria where Ca^{2+} transfer and exchange of phospholipids takes place [128, 130–133]. IP$_3$Rs form complexes with voltage-dependent anion channel 1 (VDAC1) located in the mitochondrial outer membranes through a chaperon protein Grp75 [134, 135]. Ca^{2+} released from IP$_3$Rs flows into mitochondria through VDAC and mitochondrial Ca^{2+} uniporter (MCU) located in the mitochondrial inner membranes [136, 137]. Ca^{2+} transfer from ER to mitochondria through MAMs regulate cell death and survival in cancer cells (Fig. 5). IP$_3$R-mediated Ca^{2+} release plays pivotal roles in apoptosis pathway [138–141]. Excessive Ca^{2+} influx into mitochondria causes opening of mitochondrial permeability transition
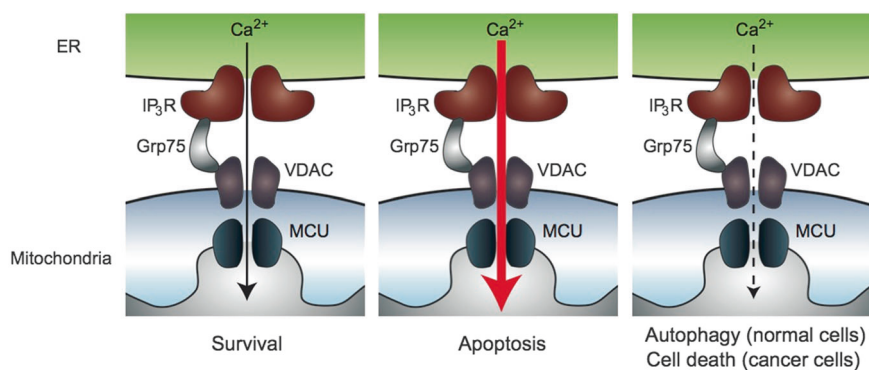

Fig. 5 Ca^{2+} transfer from ER to mitochondria at the MAM sites. Ca^{2+} released from ER through IP$_3$Rs flows into mitochondria matrix through VDAC in the outer mitochondrial membranes and MCU in the inner mitochondrial membranes. Optimal levels of Ca^{2+} transfer to mitochondria is necessary for mitochondrial metabolism and energy production (left). Excessive Ca^{2+} flux into mitochondria results release of pro-apoptotic proteins into cytosol, and results in apoptosis (middle). Suppression of basal mitochondrial Ca^{2+} uptake induces reduction in ATP production and autophagy in normal cells. Autophagy is not enough for survival of cancer cells (right) [155]

pore that results in inhibition of oxidative phosphorylation, production of reactive oxygen species (ROS), and loss of mitochondrial membrane integrity [142]. This leads to the release of pro-apoptotic proteins such as cytochrome c from mitochondria into cytosol. Cytochrome c triggers the sequential activation of caspases, resulting in apoptotic cell death. Cytochrome c also interacts with the IP$_3$R and increases its activity, causing positive feedback amplification of apoptotic signalling [117, 143]. Suppression of the IP$_3$R activity by Bcl-2 prevents excessive Ca^{2+} transfer into mitochondria and suppresses apoptosis. Disruption of the interaction between IP$_3$R and Bcl-2 has therapeutic potentials against cancer [144, 145].

IRBIT, a new sensor for the environment interaction: novel opportunities in the tumorigenesis and apoptosis

IRBIT was discovered as a molecule that binds to the IP$_3$-binding pocket of IP$_3$R [146, 147]. In contrast, an IRBIT homologue Long-IRBIT does not interacts with IP$_3$R1 because its long N-terminal appendage inhibits the interaction [148, 149]. IRBIT is a multifunctional protein that regulates diverse proteins including Na$^+$-HCO$_3^-$ co-transporter, CFTR, Na$^+$-H$^+$ exchanger [150], CaM kinase IIα [151], and PIP kinases [152]. The N-terminal intrinsically disordered protein region of IRBIT plays critical roles in its specific target recognition. Therefore, IRBIT works as a nexus of cell signaling. In addition, a member of Bcl-2 family proteins, a group of proteins that control the apoptosis, has been revealed to associate with IRBIT [153]. Bcl2l10, one of the anti-apoptotic proteins belonging to the Bcl-2 family, binds to a part of the IP$_3$-binding domain distinct from the IP$_3$ binding pocket. Bcl2l10, anti-apoptotic factor, and IRBIT interact and exert an additive inhibition of IP$_3$R. The interplay between IRBIT and Bcl2l10 is involved in regulation of apoptosis. These proteins associate in a complex in MAMs for Ca^{2+} transfer between ER and mitochondria. When apoptotic stress is added, IRBIT is dephosphorylated and released off with Bcl2l10 from the IP$_3$Rs thus the enhancement of Ca^{2+} transfer from ER to mitochondria occurs and promotes apoptosis. In addition IRBIT was reported to suppress ribonucleotide reductase in higher eukaryotes [154] working as a tumor suppressor. These data strongly suggest that IRBIT as a new regulator of cell death [155]

Mechanisms: how genetic alterations induce susceptibility to specific carcinogens

Specific genes appear to have more prominent roles in different tissue and they influence susceptibility to specific carcinogens, ensuing in a specific spectrum of different cancer types that characterize the different cancer syndromes. Accordingly, some genetic mutations cause certain tumour types, some instead are associated with a wider spectrum of cancers. For example, the Lynch syndrome, the most common among cancer syndromes, can be caused by mutations of several genes, MLH1, MSH2, MSH6, PMS2, and EPCAM, and it is characterized by a prevalence of colorectal carcinomas (lifetime risk varies between 40–80% depending on the underlying condition), although other tumour types may develop. In this cancer syndrome, genetic mutations and chronic inflammation work in concert in causing malignancy, although the exact mechanisms remain to be elucidated. BRCA1 and BRCA2 mutations lead mostly to an excess of breast and ovarian carcinomas (lifetime risk is ~ 50%) while other tumour types are also observed, but less frequently. TP53 mutations lead to the Li-Fraumeni cancer syndrome, characterized by an excess of almost any cancer type, particularly breast cancers (in women), leukaemias, sarcomas, and adrenocortical carcinomas. BAP1 mutations have also a wide spectrum of tumour types, as they give rise to the BAP1 cancer syndrome characterized by an excess of mesothelioma, eye and skin melanomas, all types of cutaneous carcinomas, renal cell carcinomas and sarcomas, while other cancer types are rare. To date, all known members of families affected by the BAP1 cancer syndrome who inherited BAP1 mutations have developed one or more cancers in their lifetime [46].

Studies of the BAP1 cancer syndrome have elucidated how reduced BAP1 levels increase susceptibility to environmental carcinogens. BAP1 is a deubiquitylase that regulates DNA repair by homologous recombination [156, 157]. It was found that BAP1 has a dual nuclear and cytoplasmic activity. In the cytoplasm BAP1 deubiquitylates and stabilizes the IP3R3 channels, the channels that control the release of Ca2+ from the endoplasmic reticulum to the mitochondria, resulting in increased intra-mitochondrial Ca2+ levels and consequent apoptosis. Exposure of normal cells derived from donors carrying inherited heterozygous germline BAP1 mutations to asbestos, UV light, and ionizing radiation-induced increased DNA damage in BAP1$^{+/-}$ cells, compared to normal cells; the damage could not be properly repaired because of the reduced levels of nuclear BAP1 and impaired DNA repair. Reduction (+/−) or absence (−/−) of BAP1 in the cytoplasm lead to a significant reduction of IP3R3 receptor channels due to the unopposed activity of the ubiquitin ligase and consequent degradation of the IP3R3 receptor by the proteasome. Thus, although these cells accumulate mutations, they cannot execute apoptosis due to reduced Ca2+ levels in the mitochondria. This resulted in significantly increased cellular transformation of BAP1$^{+/-}$ cells compared to control wild-type cells following

exposure to these environmental carcinogens, an effect that was reversed upon transfection of wild-type BAP1 into mutant cells [125].

Malignant growth is facilitated by the additional discovery that "normal" primary cells from individuals carrying germline BAP1 mutations derive energy through aerobic glycolysis and thus display a set of metabolic alterations known as "Warburg effect" which to date has been considered a hallmark of cancer cells. Thus, the Warburg effect does not always occur as an adaptive process that follows carcinogenesis, but may also predate by many years, and probably facilitate, carcinogenesis. Therefore, cells from BAP1 mutation carriers do not need to go through a selection process that favours the emergence of clones with a Warburg effect required for tumor growth: $BAP1^{+/-}$ cells constitutionally derive a large part of their metabolism through aerobic glycolysis. Thus when these cells develop mutations they are already primed for cancer growth [158].

In summary, BAP1 modulates Ca2+-dependent apoptosis and cell death via deubiquitylation of IP3R3 and, by regulating IP3R3 stability, and BAP1 also regulates cellular metabolic pathways. The cytoplasmic BAP1 activities, in concert with nuclear BAP1, modulate the high incidence of cancer in BAP1+/− carriers (100% cancer incidence during lifetime) and increase BAP1 null cancer cells resistance to chemotherapy [159].

Recent studies have elucidated how BRCA1 mutations cause breast and ovarian carcinomas (85). It was found that the interaction of BRCA1 with its partner BARD1 is necessary to recruit the exact genetic sequence needed to repair breaks in DNA caused by endogenous stress and environmental insults such as radiation exposure.

Tumour heterogeneity as the basis for acquired resistance in non-small cell lung cancer and glioblastoma: anti-cancer treatments as novel environmental interactors

Non-small cell lung cancer (NSCLC) is one of the most complex malignancies, largely due to tobacco-induced carcinogenesis. In NSCLC, TP53 mutations are very frequent, and the involvement of G × E interactions and p53 mutation spectrum in human lung cancer has long been studied [160]. Studies of G × E interactions in NSCLC have also identified other SNPs modulating the risk of tobacco-induced lung (and other) cancers [161–163]. Besides its association with tobacco, NSCLC is also well–recognized for a variety of treatable single driver oncogene-related subsets. Most prominent are activating mutations in the epidermal growth factor receptor (EGFR) and gain of

function fusions in the anaplastic lymphoma kinase (ALK) or ROS1 genes, all of which are treatable with the corresponding tyrosine kinase inhibitors (TKIs) [164, 165]. Moreover, NSCLC is characterized by a remarkable degree of inter- and intra-patient tumour heterogeneity [166].

Tumour heterogeneity contributes to difficulty in initial diagnostic testing and in determining mechanisms of de novo and acquired resistance after oncogene-targeted therapies. In the subset of patients with the most treatable NSCLC (EGFR-, ALK- and ROS1-driven) response rates in each of these categories approximate 60–70% at most [164]. In the remainder of cases, de novo (primary) resistance is present, despite harbouring identical sensitizing mutations or fusions as in the responding cases. In the case of EGFR–mutated lung cancer, randomized trials against chemotherapy have demonstrated both higher response rates and improved disease control rates [167–171]. However, despite clear benefits for TKI therapy over chemotherapy in these settings, the eventual emergence of acquired resistance and progressive disease is universal. Furthermore, complete responses, typically thought of as the first step toward cure, are rarely achieved even with these targeted therapies.

Glioblastoma (GBM) is another prototype of multiclonal, highly heterogeneous tumour in which activating mutations or amplifications of Receptor Tyrosine Kinases (RTKs), such as EGFR, have major roles in the development and progression of the malignancy. Notably the degree of heterogeneity in GBM includes also key genetic alternations, such as the oncogenic EGFR variant III (EGFRvIII) [172, 173]. Oncogene amplification in extrachromosomal DNA (ecDNA) is a recently discovered mechanism adopted by GBM to maintain the cell-to-cell genetic variability that drives tumour progression and drug resistance [174]. Amplification of driver oncogenes in ecDNA results in increased transcript level. Mathematical modelling predicted that ecDNA amplification increases oncogene copy number variation compared to chromosomal amplification and effectively favours intratumoural heterogeneity and plasticity. Dynamic modulation of ecDNA context provides a powerful ability to the tumour to readapt to, and survive, oncogene-targeting therapies.

Recently, improved methodologies for distinguishing mechanisms of resistance, such as next-generation sequencing (NGS) of tumour tissue and/or plasma cell-free DNA, have become commercially available and clinical applicability has been established [166, 175, 176]. Further, these tools have been incorporated into large-scale clinical trials employing NGS in order to match patients with genotypic therapies targeting abnormalities within their tumours, such as the Lung-MAP study (NCT02154490). Moreover, determination of secondary mutations and/or bypass track mechanisms of acquired resistance are transforming the

therapeutic landscape and directly influencing treatment decision-making [176]. The implementation of these techniques at the level of single cell resolution will allow a full characterization of the events associated with tumour heterogeneity and plasticity.

The rapid translation of new technologies into the clinic offers the potential for truly transformative approaches to cancer therapy consistent with the goals of personalized or precision medicine. In order to accomplish this, a deeper understanding of the relational complexity among germline genetic variants, acquired cancer mutations, 'non-iatrogenic' environmental factors and 'iatrogenic' environmental factors such as anti-cancer treatments is required.

Carbon source metabolism in acute myeloid leukaemia: gene × micro-environment interactions

G × E interaction studies have been proposed in some haematological malignancies [177]. Despite the absence of well defined G × E interactions, recent findings indicate that acute myeloid leukaemia (AML) may represent a valid study case for G × micro-E interactions, and help design novel specific therapies.

There are a variety of AML subtypes and several gene mutations are involved in the leukaemogenesis process. These include class I mutations which induce cellular proliferation, class II mutations which compromise normal differentiation [178], and a third class of genes encoding epigenetic modifiers, such as DNMT3A, IDH1, IDH2, and TET2 [178, 179]. Recent studies showed that these mutations are critically linked to aberrant metabolic phenotypes in AML pathogenesis and progression [180, 181]. A hypoxic microenvironment promotes the metabolic transformation to glycolytic phenotype of normal non-proliferating cells via the HIF-1 pathway, and progression of AML has been linked to the expansion of hypoxia in the subendosteal bone marrow niche relative to normal bone marrow [182]. AML cells display a significantly enhanced glycolytic metabolism [183], which was linked to poor survival in patients via contribution to Ara-C resistance in a clinical metabolomics study [181]. Increased glycolytic flux in AML cells accelerates glucose consumption and leads to glucose insufficiency in the bone marrow. Such a low-glucose microenvironment triggers a metabolic reprogramming in AML cells, with substantially increased expression of the fructose transporter, GLUT5 (SLC2A5), and thus, the ability of utilizing fructose to promote tumour cell growth relative to normal cells [184]. Fructose is the second most abundant blood sugar in human beings with a physiologically normal range of 0.5-1.0 mM [185, 186]. Fructose has previously been reported to alter the glycan structures on the cell surface of tumour cells and increase their proliferative and invasive properties when compared to glucose in vitro [187].

These evidences demonstrate that G × micro-E interactions play a critical role in accommodating energy stress and programming a new metabolic phenotype with enhanced fructose utilization in AML, leading to exacerbated leukemogenesis, as well as poor clinical outcomes regardless of the concentration of glucose present. Targeting the fructose pathway may lead to novel specific therapies for AML [184].

Obesity, metabolic syndrome and cancer

Lifestyle influences type and extent of exposure to extrinsic factors (Fig. 3). Reduced physical activity and high caloric intake have been recognised as risk factors for several malignancies [188]. In Western countries obesity is an epidemic, with one in three adult classified as obese. Despite epidemiological evidence indicating a clear relationship between obesity and oncologic conditions; the underlying molecular aspects determining the interaction between genetic predisposition, lifestyle, and metabolism have not been elucidated.

Adipose tissue contributes to maintenance of energetic balance in the organism engaging a complex network of systemic signalling that coordinate nutrient homeostasis. The excess of lipid storage alters the physiological metabolic balance of central and peripheral organs promoting constitutive signalling that communicates nutrient excess. The result of this process can include chronic hyperinsulinemia and aberrant adipokine signalling that eventually result in lower physiological defences against tumour development and progression. Hyperinsulinemia correlates with higher tumour incidence in humans [189, 190], and mouse studies have demonstrated that a high level of insulin triggers tumour progression in models such as c-Myc driven breast cancer [191]. Obesity can directly influence tumour growth, providing excess of energy and, also directly sustaining mitogenic signalling. The phosphatidylinositol 3-kinase (PI3-K) pathway is a component of the cellular insulin signalling transduction, physiologically contributing to an increase in glucose uptake in fat, liver and muscle cells by activating transcription, translation and membrane translocation of glucose transporter [192, 193]. Hyper-activation of insulin signalling leads to an unbalanced PI3-K pathway that in turn sustains aberrant cellular proliferation influencing cancer cell properties (Fig. 6) [194]. As a consequence the mutational status of this pathway in cancer cells enhances the ability of serum insulin to stimulate tumour growth, thereby playing a critical role in the response of the tumour to the obese status [195]. PI3-K
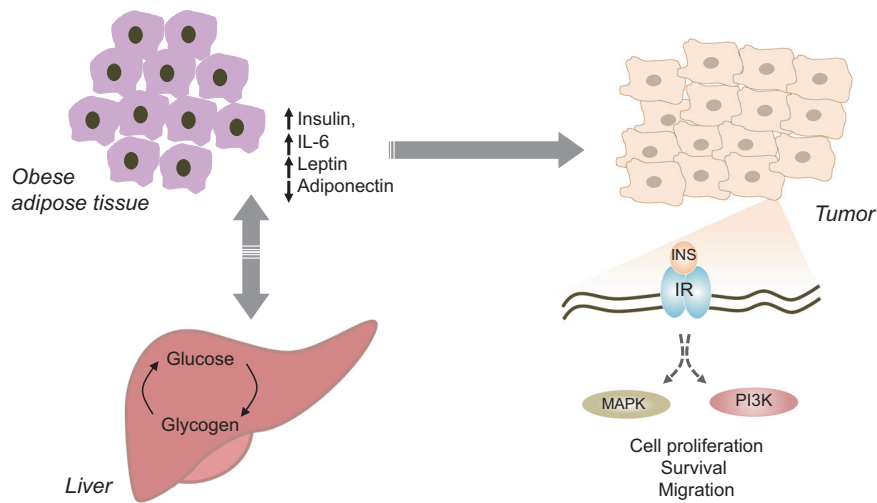
Fig. 6 Obesity and hyperinsulinemia influence cancer development and progression. Accumulation of adipose tissue in obesity systemically alters metabolic homeostasis, affecting endocrine signalling between organs and leading to condition such as chronic hyperinsulinemia. Insulin activates signalling pathways, including PI3-K and MAPK, which are generally required to sustain cancer cells. Overall these mechanisms might both contribute to reduction of physiological barriers against tumour ormation and promote cancer progression

inhibitors acutely induce insulin resistance in liver and muscle and result in elevation in serum glucose, and consequent elevation in serum insulin. Therapies that lower serum glucose and insulin, especially a ketogenic diet, could conceivably improve responses to PI3-K inhibitors, even in tumours carrying no mutations in the pathway.

There is substantial evidence in support of an implication of obesity in human cancer development [188], however it is still difficult to define a clear causative connection between the events. Many aspects associated with obesity, such as hyperinsulinemia, inflammation, endocrine signalling, have been independently associated to cancer [196]. It will be important to define whether obesity per se represents a risk factor or the hypercaloric diet, and whether the composition of the diet is associated with increased susceptibility to cancer.

Myelodysplastic syndromes, haematological malignancies and post-transcriptional control of gene expression

Chronic lymphocytic leukaemia (CLL) is the most common human leukaemia. Contributing environmental risk factors have not yet been identified yet; however, genetic predisposition appears very likely [197]. The loss of microRNA (miR)-15/16 on human chromosome 13q14 is the most common genetic alteration in CLL [198]. Physiologically, miR-15/16 regulates the expression of BCL2 [199], which plays an important part of the p53 signalling pathway, and that when overexpressed causes follicular cell lymphoma and CLL. Loss of miR-15/16 leads to BCL2 overexpression and CLL.

In addition to loss of miR-15/16 in CLL, deregulation of expression and processing of microRNAs has been observed in cancer. During transformation, cancer cells acquire clusters of enhancers, called super-enhancers (SEs). This class of regulatory elements is able to drive higher levels of transcription than typical enhancers. The acquisition of SEs boosts expression of oncogenes, favouring the establishment of the tumour phenotype. SE constituents act cooperatively and facilitate Drosha/DGCR8 recruitment and pri-miRNA processing to boost cell-specific miRNA production. During cancer progression SEs form at the miRNAs genes, enabling a co-transcriptional Drosha/DGCR8-dependent microRNA processing [200, 201].

Myelodysplastic syndromes (MDS) and leukaemia present a relatively high frequency of mutations in genes encoding proteins that function in, or regulate, splicing of mRNA precursors [202]. Cancer cells take advantage of deregulated mRNA splicing to produce aberrant proteins with added, deleted, or altered functional domains that contribute to malignancy, or else splicing errors can lead to protein loss-of-function. CRISPR/Cas9 introduction of the MDS-associated P95H mutation in the serine/arginine-rich splicing factor 2 (SRSF2) in K562 leukemia cells influences about 1% of total splicing events, very similar to the extent of splicing deregulation in MDS patients with the same mutation. Mutant SRSF2 does not lose its functionality but rather binds more tightly than its wild-type counterpart to RNA sites containing UCCAG while binding less tightly to UGGAG sites, thereby increasing or decreasing, respectively, inclusion of target exons [203]. Hence, mutations of spliceosomal genes contribute to the cancer phenotype, resulting in deregulated or aberrant splicing of specific mRNA precursors.

Precision medicine and targeted therapies

It may take a very long time for a research finding in the laboratory to make its way to the patient. For example, it took 32 years from Dr. Croce's discovery of the critical role of the BCL2 gene in CLL to FDA approval in 2016 of an anti-Bcl2 drug for CLL. The anti-Bcl2, BH3 mimic, ABT199 or venetoclax, induces massive lysis of CLL cells: 80% of CLL patients respond to the drug with 85% showing responses lasting over 1 year, including complete remissions without evidence of minimal residual disease [204, 205].

Conventional cancer therapy kills cancer cells by causing DNA damage. However cancer cells are often deficient at least in one of the DNA repair mechanisms. Profiling the DNA repair pathways in patients might help in predicting radiation/chemotherapy responsiveness and therefore would help in designing personalised treatments. The Fanconi Anemia Gene D1, BRCA2, participates in homologous recombination (HR) repair and it is also linked to familial breast and ovarian cancer [206]. BRCA2-deficient epithelial ovarian cancers (EOCs) contain upregulated DNA polymerase θ (Polθ), a DNA polymerase, which promotes a compensatory Alternative end joining (Alt-EJ) DNA break repair. Synthetic lethality in mice between the Polθ and HR pathway and hypersensitivity of HR-deficient tumour to Polθ inhibition indicate a potential novel therapeutic approach for cancer with HR-inactivation, such as familial BRCA2 [207]. A successful example of exploiting synthetic lethality in cancer therapy is the development of inhibitors of poly ADP-ribose polymerases (PARPs), which selectively kill cancer cells with defective DNA repair, especially in breast and ovarian cancer patients with mutations in BRCA1 and BRCA2 [208].

While DNA repair deficiency contributes to cancer development by causing more genetic mutations, such deficiency can be harnessed for cancer immunotherapy because these mutations are expected to generate more neoantigens for recognition by the immune system. For example, patients with mismatch repair deficiency showed dramatic responses to PD-1 antibody treatments [209]. Such dramatic results have led to the recent approval by FDA of immune checkpoint blockade therapies for any solid tumors based on molecular diagnosis of mismatch repair deficiency (microsatellite instability) rather than tumor types.

The design of targeted therapies often clashes with the difficulty of targeting novel protein complexes, but computational tools have been developed to identify druggable binding sites. In the human proteome the number of potentially druggable protein–protein interactions is extremely wide and largely exceed the human kinome. The generally large, flat, and relatively featureless binding sites of protein complexes make drug design very difficult by conventional approaches. Methods that integrate conventional methods to identify druggable areas at the protein surfaces together with sequence co-evolution tools used to identify protein–protein surfaces are now making it possible to overcome this challenge [210]. Success of this approach has been demonstrated on how the NEET family, a relatively new class of three related [2Fe-2S] proteins (CISD1-3), important in human health and disease, particularly cancer [211]. Protein levels of NAF-1 (CISD2), mitoNEET (CISD!) are elevated in human epithelial breast cancer cells, and their suppression by shRNA results in significantly reduced cell proliferation and tumour growth [212]. Structural studies and computational approaches led to identification of a small molecule named MAD-28 as an inhibitor of NAF-1 and mitoNEET. MAD-28 has been proven to selectively kill breast cancer cells, without apparent effect on normal epithelial cells and represents a potential alternative anti-cancer approach [213].

Conclusion

On the lengthy issue of cancer origin, with the 'bad-luck' vs 'toxic insults' contest, it should be considered that the exact evaluation of the number of stem cells and the mathematical model used are crucial points [3]. In fact, the number of stem cells may well vary during life, and their evaluation has been accounted for using different methods that are not directly comparable. On the other hand, if we accept that extrinsic risk factors are the main drivers of cancer, we should question the yet unidentified extrinsic risk factors that drive the cancer types for which such factors have not been identified [4].

The initiating events should be further investigated, for example spontaneous mutations and stem cell markers in different tissues at different ages. Indeed, despite a stable balance between the degree of DNA damage and the subsequent repair being maintained throughout life, there is a constant accumulation of genetic mutations with age in human adult stem cells, with a rate of circa 40 mutations/ year, mostly unrelated to the large variation of cancer incidence in a specific tissue [214]. On the other hand, human cancers show very different rates and patterns of somatic mutations, which could be categorised in 21 general signatures [215]. An unbiased forward genetic approach using a mouse mutagenic program, along the lines as the one developed by Dr. Beutler that led to the identification of the Toll-like receptors (TLRs) as well as many other molecules with non-redundant function in the immune response, may help us identify mutations responsible for both quantitative and qualitative phenotypes to understand

the mechanism by which certain mutations contribute to cancer development [216].

A landmark advance to evaluate the lifelong susceptibility to cancer has been allowed by the use of selective Cre-recombination of conditional lineage tracing in stem cells of mouse organs. By using CreER2-recombinase and LacZ from the endogenous Prom1 (Cd133) locus, activated with a tamoxifen-induced Rosa-ZsGreen fluorescence protein lineage tracing allele, Zhu et al. showed that tumour incidence is determined by the lifelong generative capacity of mutated cells, rather than the initiating mutation or the proliferative capacity: a combination of stem cell mutagenesis and extrinsic factors leading to a 'perfect storm' from which cancer arises [217]. A mutation analysis shows that only 18% of mutations occurred in oncogene/tumour suppressors, whilst 82% of mutations were in other genes, including genes regulating immune-surveillance and epigenetic modifiers consistent with random mutation theory [217].

A recent paper by Tomasetti et al. tried to clarify the contribution of random replication errors, environmental factors and heredity, emphasising the difference between aetiology of cancer mutations and cancer prevention [218]. These authors proposed that most cancers are preventable, as mutations dependent on environmental factors –even though numerically less prevalent than those dependent on random replication errors or hereditary—still contribute to cancer development, and their absence would result in prevention of a large number of cancer cases.

The current hypothesis is that while intrinsic random DNA errors are the most frequent type of mutations in all tissues and cells, including stem-cells, development of cancer is often facilitated and accelerated by the combinatory effect of these "inevitable" errors—as cells accumulate about 3 new mutations/cell division, together with those caused by exposure to mutagenic environmental carcinogens and hereditary mutations.

Compliance with ethical standards

Conflict of interest M.C. has pending patent applications on BAP1; H.I.P., has patents pending for use of fibulin-3 for diagnosis of mesothelioma; M.C., H.Y and H.I.P. have patents pending for use of HMGB1 for diagnosis of mesothelioma; M.C. and H.Y. have patents pending for use of HMGB1 and its isoforms for diagnosis of mesothelioma; M.C. provides cost-free consultation for MM expertise and diagnosis to patients and colleagues and paid medical-legal expertise. The remaining authors declare that they have no conflict of interest.

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