Review: the Contribution of both Nature and Nurture to Carcinogenesis and Progression in Solid Tumours

Published in Cancer Microenvironment

Iain Joseph Hyndman[1,2]

i.hyndman@dundee.ac.uk

1. College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK
2. Present address: Ninewells Hospital & Medical School, University of Dundee, Dundee

IJ Hyndman was affiliated with the University of Glasgow at the time of writing.

Abstract

Cancer is a leading cause of mortality worldwide. Cancer arises due to a series of somatic mutations that accumulate within the nucleus of a cell which enable the cell to proliferate in an unregulated manner. These mutations arise as a result of both endogenous and exogenous factors. Genes that are commonly mutated in cancer cells are involved in cell cycle regulation, growth and proliferation. It is known that both nature and nurture play important roles in cancer development through complex gene-environment interactions; however, the exact mechanism of these interactions in carcinogenesis is presently unclear. Key environmental factors that play a role in carcinogenesis include smoking, UV light and oncoviruses. Angiogenesis, inflammation and altered cell metabolism are important factors in carcinogenesis and are influenced by both genetic and environmental factors. Although the exact mechanism of nature-nurture interactions in solid tumour formation are not yet fully understood, it is evident that neither nature nor nurture can be considered in isolation. By understanding more about gene-environment interactions, it is possible that cancer mortality could be reduced.

Keywords

Cancer · Carcinogenesis · Mutations · Gene-environment · Oncogenes · Tumour suppressor genes

Introduction

Cancer is one of the leading causes of death worldwide. In 2012 there were a reported 8.2 million deaths attributable to cancer [1]. Over the past half of a century, research has shown that cancer arises as a result of alterations to DNA. These somatic mutations provide a cell with attributes that enable it to bypass the regulatory mechanisms that control normal cell growth and proliferation. These traits – termed the "Hallmarks of Cancer" [2] – allow a cell to proliferate abnormally and confer the potential for growth at sites distant to the primary tumour. Key hallmarks include: sustained proliferation and immortality; evasion of apoptosis and growth suppression; genome instability; induction of angiogenesis and inflammation; invasion and metastasis [3]. "Cancer" is a broad term encompassing over 200 distinct diseases [4] which are unified by the common principle of uncontrolled cell growth and metastatic potential. However, cancers differ vastly in their aetiology. Some cancers share common mutations and risk factors; however, there are many cancers that would be better described as distant cousins than siblings. The broad variation in cancer aetiology has implications when trying to address the question "*What causes cancer?*" Sporadic mutations commonly arise and accumulate as a result of exposure to environmental carcinogens, whilst rare hereditary cancer syndromes often arise as a result of an inherited mutation with little to no environmental input [5]. It is widely accepted that the majority of cancers arise through a complex series of interactions between genes ("**nature**") and the environment ("**nurture**"). Theses interactions vary between individuals, genders and ethnicities [6]. This variation explains why not everyone who is exposed to the same environmental factors will develop cancer. It is estimated that 95 % of cancers are explained by the environment interacting with genes with the remaining 5 % of cancers explained by genetics alone [7]. Whilst there are many known environmental and genetic factors which play a part in the development and progression of solid tumours (carcinogenesis), it is difficult to identify and quantity the role that each factor plays. This review focuses on the mechanism by which genetic and environmental factors contribute to carcinogenesis and explores the complex mechanisms of key gene-environment interactions.

Models and Stages of Carcinogenesis

Natural Selection

During carcinogenesis, a cell acquires a series of genetic mutations. The process by which the mutated cell gives rise to cancer is frequently compared to Darwin's theory of evolution, whereby cells with mutations which confer increased replicative and survival abilities are 'selected' to survive. Selected cells that acquire enough mutations so as to confer autonomy may go on to form malignant tumours. Additionally, cells that acquire a limited number of mutations may foster benign tumours. As the number of somatic mutations that a cell has acquired increases, the chance of tumour formation also

increases. In some cell types that already show evidence of neoplasia (abnormal growth), the rate of acquisition of further mutations is increased. This increases the chance for an already-mutated cell to acquire the additional genetic alterations which are necessary for the formation of a solid tumour [8].

Tumour Initiation and Promotion

Tumour development and progression is known to be a stepwise process occurring over a variable period of time. The first steps in tumour development are initiation and promotion [9]. Initiation may occur spontaneously or be caused by an endogenous or exogenous mutagen (such as reactive oxygen species or tobacco smoke respectively) [10, 11]. In the context of skin cancer, initiating agents include environmental chemical carcinogens and UV light [12]. Initiating agents cause damage to DNA and can therefore activate proto-oncogenes (such as *KRAS*) and inactivate tumour suppressor genes (TSGs), such as *TP53*. However, initiation will not give rise to a cancer on its own: a promoting agent is needed. A promoter is a compound which has little to no carcinogenic effect in isolation but has the ability to promote tumour growth when applied subsequent to an initiating factor [9]. When skin is repeatedly exposed to a promoter (such as UV light or certain chemicals), proliferation of the initiated cell is stimulated [12]. Promoting agents cause initiated cells to clonally expand without affecting neighbouring uninitiated cells [10]. The classic model used to identify the role of tumour initiators and promoters is the mouse skin model of chemical carcinogenesis. In this model, a single low dosage application of 7,12-dimethylbenz[a]-anthracene (DMBA; a component of tar) followed by treatment with the promoter 12-*O*-phorbol 12-myristate 13-acetate (TPA) leads to the formation of skin carcinomas. TPA interacts with Protein Kinase C (PKC) which activates the mitogen-activated protein kinase (MAPK) pathway. Activation of the MAPK pathway drives cell proliferation (see Fig.1) [10, 13]. The mouse skin model has since been used to study defects in genes and signaling pathways at different stages of tumour development. Tumour promotion is also driven by inflammatory cytokines. This mechanism was first demonstrated using mouse models of colon, skin and liver cancer. Cytokines activate transcription factors (such as STAT3, NF-ºB and AP-1) which in turn promote transcription of key proliferation and survival genes (see Fig.1) [14].

Tumour Progression and Metastasis

Tumour progression and metastasis occurs as a result of further genetic alteration, such as changes in gene expression [12]. The ‘metastatic cascade’ refers to the process which results in cancer cells spreading from their primary location to a distant site. These steps include: proliferation, angiogenesis, detachment/local invasion, entry to and exit from circulation (intravasation and extravasation respectively) and growth at a distant site [15]. For a cell to invade locally and subsequently metastasise, it must first undergo alterations which give it a more invasive phenotype. These changes include upregulation of proteases (allowing the cell to invade through structures such as the extracellular matrix and the basement membrane) and downregulation of cell-to-cell adhesion molecules

(allowing the cell a greater degree of motility) [16]. The relative infrequency of metastasis suggests that metastatic deposits arise from rare cells within the primary tumour which have the ability to successfully colonise distant sites within the human body. This concept is termed “metastatic inefficiency”. There are ongoing efforts by some groups to find genes specifically involved in metastasis. However, it has also been argued that these genes do not exist and that metastasis instead arises as the result of mutations in well-known TSGs and oncogenes. The heterogeneity between different cancers (and between the same cancer in different patients) means that both theories may be true. Indeed it is well known that there are many different paths that a cell can take to become a cancer [17].

The Role of Nature in Carcinogenesis

Somatic Mutations

It is known that the somatic mutations that result in cancer formation arise due to damage by endogenous and exogenous factors. Mutations in a cancer cell are classified by the nature of the resulting DNA sequence change. These changes can be relatively small such as insertions, substitutions and deletions of a short segment of DNA or they can be larger changes, such as an increase or decrease in the number of chromosomes found in normal diploid cells. It should be noted that the majority of damage to DNA is repaired [8]. Somatic mutations within a cancer cell can be classified as either driver or passenger mutations. Driver mutations offer a selective growth advantage to a cell. Passenger mutations do not offer a growth advantage but were present in the cell at the time of acquisition of a driver mutation. It is thought that driver mutations represent only a small proportion of the total number of mutations within a cancer [18]. It is probable that most cancers possess more than one driver mutation and that this number will vary between different cancers. It has been suggested that 5–7 driver mutations are required for the formation of some solid tumours, such as breast, prostate and colorectal [8]. In non-small cell lung cancer, for example, several driver mutations have been identified including mutations in *ALK, EGFR, HER2, BRAF, KRAS, MET, PIK3CA, MAP2K1* and *AKT1* [19].

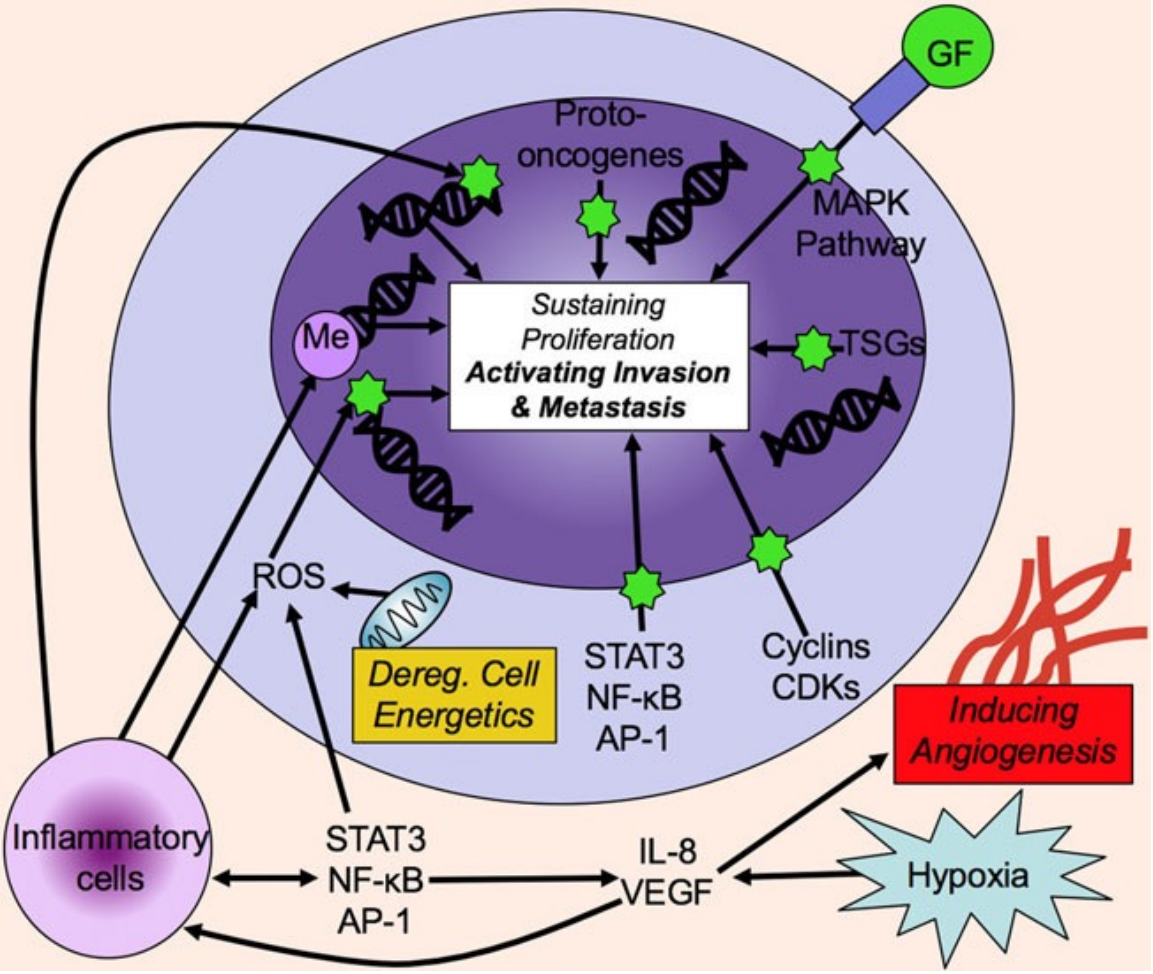

Fig. 1 Factors contributing to the acquisition of the *hallmarks of cancer* in a solid tumour cell. This schematic shows only some of the critical and complex interactions involved in carcinogenesis. Mutations in genes coding for key regulators of cell cycle, growth and proliferation (green stars) arise due to insult from both exogenous and endogenous sources. These mutations (*genetic instability*) are likely to work synergistically to produce a solid tumour. *Tumour promoting inflammation* plays a key part in tumour development and has a role in *sustaining proliferation* and in *activating invasion and metastasis*. STAT3, NF-ºB and AP-1 are transcription factors found within tumour-associated macrophages (TAMs), the tumour microenvironment and the tumour cell itself which lead to the activation of IL-8 and VEGF. IL-8 and VEGF are also activated by hypoxia and play key roles in *inducing angiogenesis*. (Me) = gene promoter methylation which can result in silencing of TSGs. (GF) = growth factor binding to its receptor and activating the MAPK pathway, resulting in cell proliferation. ROS = reactive oxygen species, shown here to be produced by mitochondria in the cytoplasm as part of normal cellular metabolism. (*Deregulation of cellular energetics* [*Dereg. Cell Energetics*] is also depicted, whereby the tumour cell switches from aerobic respiration in the mitochondria to anaerobic glycolysis within the cell cytoplasm. This metabolic alteration is thought to play a role in carcinogenesis)

Cell Cycle

The cell cycle is the series of steps that a cell must progress through in order to proliferate. It is tightly controlled by several important checkpoints. These checkpoints assess DNA damage, cell size and extracellular growth signals and ensure that damaged DNA is not passed on to prospective daughter cells. If an abnormality is detected, the cell will arrest at G1 or G2 checkpoints until the damage is repaired. Cyclins and cyclin-dependent kinases (CDKs) are key regulators which govern progression through the cell cycle. Mutations in either cyclins or CDKs can allow a mutated cell (which should have arrested at a checkpoint) to continue through the cell cycle, leading to the formation of two daughters cells which also possess the damaged DNA [23]. This is a key step in solid tumour formation. The tumour suppressor protein p53 (known also as the "guardian of the genome") is able to induce cell cycle arrest. p53 is also involved in the repair of DNA, senescence and apoptosis. Inactivation of p53 causes a loss of tumour suppression activity within a cell, as well as a gain of survival and growth abilities as is seen in many cancers. Unchecked progression through checkpoints and evasion of anti-growth signals lead to genomic instability and contributes to the probability of metastasis [24]. Usually both alleles of a TSG have to be altered before a functional effect is seen (a recessive loss of function). The mechanism by which a TSG (such as *RB1*) suffers a recessive loss of function due to mutations in both alleles of the gene is termed the "Knudson two-hit hypothesis" [25]. *TP53* (the gene coding for p53) is an important exception to the two-hit hypothesis: a mutation in only one allele of the gene is needed for a loss of function of the normal p53 protein. Thus p53 mutations have the ability to act in a dominant negative manner. Oncogenes (such as *Ras*) need only one allele to be affected for an abnormal effect to be observed (a dominant gain of function) [2]. Oncogenes become activated when proto- oncogenes are altered in one of three ways, namely mutation, gene amplification or chromosomal rearrangement. Proto-oncogenes code for proteins which are involved in normal cell growth, differentiation and survival. Activation of oncogenes often leads to the production of a mutant protein with increased, unregulated activity [26].

The Role of Nurture in Carcinogenesis

Environmental Factors in Tumour Development and Progression

In a medical context, environmental exposures include all non-genetic exposures such as diet, lifestyle and infections [27]. Since Sir Percivall Pott first realised that environmental carcinogens could cause cancer in the 18th century (chimney soot *vis-à-vis* squamous cell carcinoma of the scrotum), many other environmental factors have been found to play a role in cancer development. These exogenous factors cause genetic alterations in addition to the changes that occur spontaneously within the cell. Known environmental mutagens include asbestos, arsenic and radon [27]. Environmental factors are known to play a role in early cancer development by causing alterations to the genome which give rise to a pre-malignant lesion [28]. The roles of environmental factors in later stages of

carcinogenesis are less well described; however, there are certain environmental factors which are likely to play a role throughout tumour development and progression. Until recently, the role of environmental agents in epigenetic change was unknown (it was thought that these agents acted exclusively by direct genomic alteration). However, it is now known that external agents can cause epigenetic alterations (especially gene promoter methylation). Epigenetic changes are functional changes to the genome of a cell, which may result in altered gene expression, without altering the primary DNA sequence itself. Gene promoter methylation can frequently lead to silencing of the affected gene. Tumour-promoting inflammation (such as that caused by cigarette smoke) can also cause epigenetic changes which lead to tumour initiation (see Fig.2) [14]. Certain dietary factors and obesity are also known to cause inflammation and have been implicated in carcinogenesis. Whilst much effort has gone in to finding genetic and environmental risk factors, there may also be a clinical benefit in identifying factors that are protective against cancer.

Cigarette Smoke

Smoking and lung cancer is perhaps the best-known example of the role of an environmental factor in carcinogenesis. Sir Richard Doll first proved this link in 1950 and since then much has become known about the diverse role of cigarette smoke in lung cancer [29]. Smoking has also been linked to a variety of other cancers (see Table 1). Smoking plays a direct role in carcinogenesis through the activation of oncogenes and the inactivation of proto-oncogenes. Smoking also indirectly contributes to carcinogenesis through impaired mucociliary clearance; activation of macrophages; increased levels of proteases and dampening of the immune system. Cigarette smoke is known to contain a multitude of toxic and carcinogenic compounds including carbon monoxide, hydrogen cyanide, ammonia and vinyl chloride [30]. Cigarette smoke also contributes to tumour promoting inflammation and can cause epigenetic changes to the genome (see Fig.2) [14].

UV Exposure

Intense ultraviolet (UV) light exposure has been implicated in the development of melanoma. UV light damage has recently been shown to account for as many as 46 % of all driver mutations in melanoma. As with cigarette smoke, the mechanistic role of UV light in cancer development is broad and includes the generation of reactive oxygen species (ROS) [31]. However, UV exposure has also been shown to play a nonmutagenic role in melanoma development through the activation of tumour-driving cell signaling pathways. Despite the evidence linking UV exposure and melanoma, the exact mechanisms behind this link remain unclear: the common genetic changes that result in *NRAS* and *BRAF* driver mutations in melanoma are not the C to T base transitions which are typical of UVB damage [32]. As with other environmental factors, it is likely that UV exposure plays a diverse role in carcinogenesis, such as in initiation and promotion [12].

Viruses

Over the past half a century, much has been discovered about the role of viruses in cancer and several cancer-causing viruses (oncoviruses) have now been identified. These viruses are known to play a role in the development and progression of human tumours. Oncoviruses are diverse in their mechanism of action and include retroviruses (human T-lymphotropic virus-I), RNA viruses (hepatitis C virus) and multiple subtypes of DNA viruses (which include Epstein-Barr virus and Human papillomavirus) [33]. HIV is also implicated in the development of some cancers (such as Kaposi's sarcoma) through induction of immunosuppression; however, the virus does not directly cause tumour growth [34]. In addition to viruses, parasites and bacteria are also known to cause cancer (for example, inflammation in the stomach due to *Helicobacter pylori* colonisation is the greatest risk factor for developing gastric cancer [35]). These infectious agents (viruses, parasites and bacteria) can be classified as either direct carcinogens (viral oncogenes expressed) or indirect carcinogens (cause mutations through chronic inflammation); however, some viruses do not fit exactly into either description and are likely to have multiple roles and interactions in cancer development [33]. There are other known environmental exposures (such as dietary aflatoxin and smoking) which act as cofactors in the induction of certain viral cancers (see Fig.2) [34].

Solid Tumour	**Nature Risk Factors**	**Nurture Risk Factors**
Bladder Cancer	Mutations in: *PRKDC*, *TP53*, *ARID1A*	Smoking, dyes
Breast Adenocarcinoma	Mutations in: *BRCA1*, *BRCA2*, *TP53*, *PIK3CA*, *MAP3K1*, *HER2;* oestrogen	Obesity, hormone replacement therapy, late menarche, having more children, radiation, alcohol
Colorectal Cancer (CRC)	Mutations in: *KRAS*, *NRAS*, *APC*, *PRKDC*, Wnt/² -catenin signaling; inflammatory bowel disease (IBD)*; genetic syndromes namely hereditary nonpolyposis CRC (HNPCC) and familial adenomatous polyposis (FAP)	Smoking, alcohol, low fibre, obesity, *H. pylori*, inflammatory bowel disease (IBD)*, obesity, red meat
Non-Small Cell Lung Cancer (NSCLC)	Mutations in: *KRAS*, *NRAS*, *TP53 ALK*, *EGFR*, *HER2*, *BRAF*, *KRAS*, *MET*, *PIK3CA*, *MAP2K1*, *AKT1*	Smoking, air pollution, radon[21]
von Hippel-Lindau Syndrome (syndrome results in haemangioblastomas, clear cell renal carcinomas and phaeochromocytoma)	Germline mutation of the von Hippel-Lindau TSG on chromosome 3p25	Environmental factors not a recognised cause of this disease
Endometrial Carcinoma	Mutations in: *KRAS*, *NRAS*, *PIK3CA*, *PIK3R1*, *ARID1A;* oestrogen	Obesity, diabetes

Table 1 Key risk factors associated with development of some solid tumours. This table demonstrates some of the key genetic and environmental risk factors for the development of some cancers. The mutations listed include DNA repair genes (BRCA1, BRCA2, TP53) and genes involved in cell growth and proliferation (KRAS, NRAS, PIK3CA, MAP3K1, MAP2K1 HER2). Note that this table is not exhaustive and there are likely to be many cancer-causing factors which are unknown at present.

*IBD itself is a disease which is caused by gene-environment interactions. [20–22]

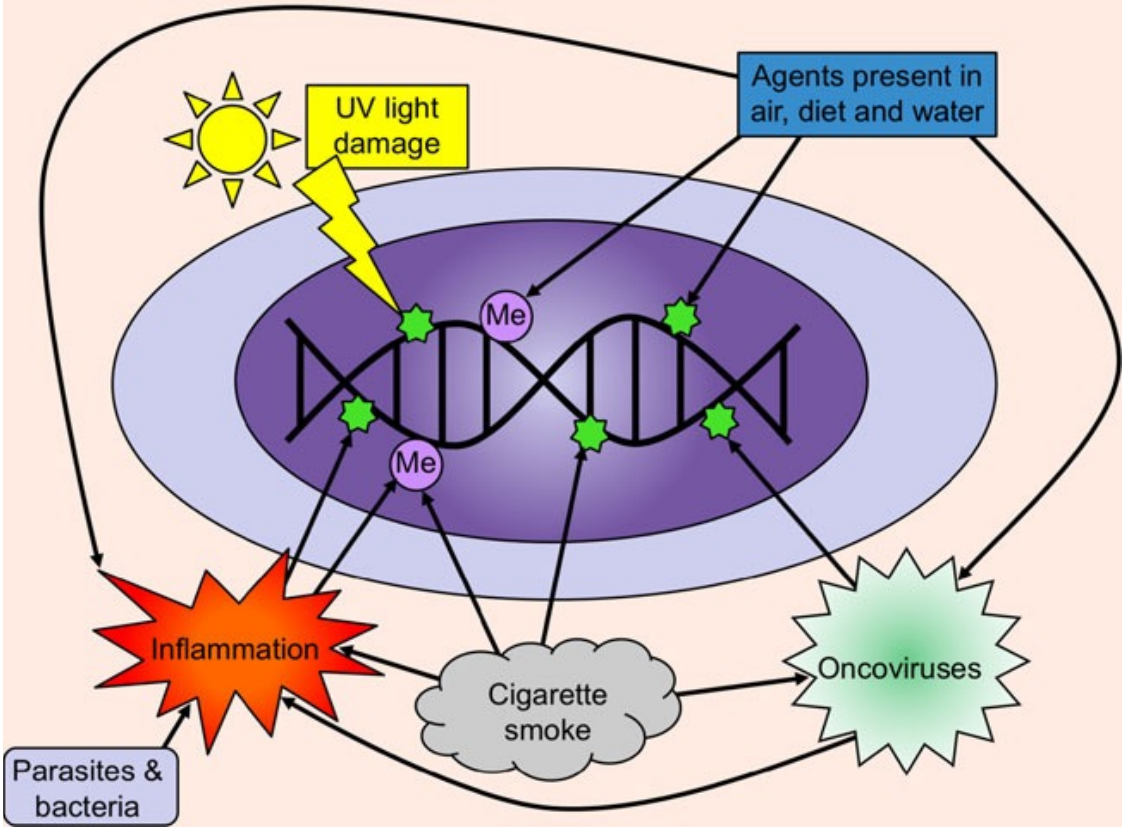

Fig.2 Environmental factors involved in the development of some cancers. There are many environmental factors that play a role in the development of cancer. As well as directly damaging DNA (green stars), environmental factors work synergistically with each other to cause mutations. Some of these interactions are shown above; however, this figure is not complete: these interactions are infinite and are potentially bi-directional. Not all of the exposures shown above are needed for cancer development. (Me) = gene promoter methylation which can result in silencing of TSGs

Nature and Nurture in Key Hallmarks of Cancer

Inflammation

Inflammation is a key hallmark of cancer [3] and both environmental and genetic factors have been shown to play a role tumour-promoting inflammation. An inflammatory tumour microenvironment (TME) is necessary for the development and progression of all solid tumours, and immune and inflammatory cells are often seen within tumours. Tumour-associated macrophages (TAMs) and T cells are amongst the most common immune cells found in the TME. These cells produce various inflammatory mediators including cytokines, chemokines and growth factors. These inflammatory components play a role in neoangiogenesis, tumour invasion and metastasis and in causing further damage to DNA. It is also thought that inflammation may play a direct role in mutagenesis [14].

Angiogenesis

At some stage in tumour development, a tumour will ‘outgrow’ its blood supply resulting in hypoxia and necrosis at the core of the tumour. These conditions drive the ‘angiogenic switch’ (the upregulation of proangiogenic factors and the downregulation of antiangiogenic factors). This change promotes new blood vessel formation (neoangionesis) and increases the likelihood of tumour metastasis [36]. Vascular endothelial growth factor (VEGF) is the primary mediator of angiogenesis [37]. These agents recruit TAMs to the site of necrosis where they produce both inflammatory and angiogenic mediators. Genes which promote angiogenesis (such as IL-8 and VEGF) are turned on by transcription factors produced by TAMS (such as AP-1, STAT3 and NF-ºB)(see Fig.1) [14]. Low concentration cigarette smoke extract has been shown to cause the release of the pro-inflammatory cytokines IL-8 and TNF-± through activation of NF-ºB and the generation of reactive oxygen species [38]. It has been shown that NF-ºB is a key component of inflammation-induced growth and progression [39]. Activation of NF-ºB in inflammatory cells causes production of inflammatory mediators. These mediators cause NF-ºB to recruit more inflammatory cells in a feed-forward loop [14]. Additionally, TNF-± [40] and IL-8 [41] have been shown to play a role in all stages of cancer growth. Cigarette smoke is also known to cause production of other inflammatory cytokines. It is likely that these inflammatory mediators will also play roles in tumour development, progression and angiogenesis.

Altered Cell Metabolism

In addition to unregulated proliferation, energy metabolism within a cancer cell also becomes aberrant at some stage during carcinogenesis. The “Warburg effect” is the process by which a cancer cell switches from aerobic respiration to anaerobic glycolysis. The exact survival benefit of this switch remains unclear given the inefficiency of glycolysis compared to aerobic respiration; however, it is thought that glycolysis plays a role in promoting cell proliferation [3]. As well as variation in environmental exposures, individuals vary also in their ability to metabolise and excrete potentially mutagenic agents. This variability is due to the existence of polymorphisms in genes coding for enzymes that are involved in key metabolic functions. Individuals with variants of enzymes which are less well able to clear damaging factors may be more likely to suffer DNA damage. These enzymes include the cytochrome P450 family which are based in the mitochondria and in the endoplasmic reticulum [5]. Variants in DNA repair enzymes have also been found to exist and to be associated with an elevated risk of some cancers [42]. These variants once again demonstrate the infinite variation and complexity of gene-environment interactions in cancer.

Challenges and Future Perspectives

Unraveling the Complexities of Nature-Nurture Interactions

Both genetics and the environment play key roles in solid tumour development and progression. The presence of gene-environment interactions in cancer has been well documented in the literature; however, the exact mechanism of these interactions remains elusive. It is clear that the interactions are extremely complex and that the role of both components cannot be considered in isolation. It is known that even human behaviours that lead to environ- mental exposures (such as smoking) are likely to be influenced by genetics. It can therefore be seen that gene- environment interactions are ‘bi-directional’: genetics pre- dispose an individual to an exposure and the exposure causes disease in the genetically predisposed individual. The possibility of ever fully understanding the mechanisms of gene-environment interactions is unknown. It is also unclear whether unraveling these exact mechanisms will result in a clinical benefit [43]. However, a survival benefit has already been gained from merely identifying such interactions. Since Doll first linked smoking to lung cancer in 1950 [29], public health campaigns have raised awareness of the health risks associated with smoking and have reduced cancer related deaths. By understanding more about gene-environment interactions, it is possible that we would be able to develop new screening tests for cancers based on known risk factors which could lead to a reduction in cancer mortality worldwide [43].

Looking ahead

Ultimately, neither nature nor nurture can be considered in isolation in carcinogenesis. Quantifying environmental exposures is difficult and wrought with inaccuracies. There is now a need for large gene-environment studies that are able to demonstrate the relationship between gene variants and environmental exposures in cancer. Indeed, perhaps it is time to toss out the old paradigm of “nature versus nurture” and replace it with a new one: “nature *and* nurture”.

References

1. Stewart BW, Wild CP (eds) (2014) World cancer report. International agency for research on cancer, Lyon

2. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100(1):57–70

3. Hanahan D (2011) Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674

4. Cancer Research UK (2013) How many different types of cancer are there? [internet] http://www.cancerresearchuk.org/about- cancer/cancers-in-general/cancer-questions/how-many-different- types-of-cancer-are-there. Accessed 22 February 2015

5. Brennan P (2002) Gene-environment interaction and aetiology of cancer: what does it mean and how can we measure it? Carcinogenesis 23(3):381–387

6. Milne AN, Carneiro F, O'Morain C, Offerhaus GJA (2009) Nature meets nurture: molecular genetics of gastric Cancer. Hum Genet 126:615–628

7. Perera FP (1997) Environment and cancer: who are susceptible? Science 278(5340):1068–1073

8. Stratton MR, Campbell PJ, Futreal PA (2009) The cancer genome. Nature 458:719–724

9. Weinstein IB (1988) The origins of human cancer: molecular mech- anisms of carcinogenesis and their implications for cancer preven- tion and treatment-twenty-seventh G.H.A. Clowes memorial award lecture. Cancer Res 48(15):4135–4143

10. Weinberg RA (2014) The biology of cancer, 2nd edn. Garland Science, New York

11. Hoffman D, Hecht SS, Wynder EL (1983) Tumor promoters and cocarcinogens in tobacco carcinogenesis. Environ Health Perspect 50:247–257

12. Rundhaug JE, Fischer SM (2010) Molecular mechanisms of mouse skin tumor promotion. Cancers (Basel) 2(2):436–482

13. Marquardt B, Frith D, Stabel S (1994) Signalling from TPA to MAP kinase requires protein kinase C, Raf and MEK: reconstitution of the signalling pathway in vitro. Oncogene 9(11):3213–3218

14. Grivennikov SI, Greten FR, Karin M (2010) Immunity, Inflammation and Cancer. Cell 140(6):883–899

15. Fidler IJ (2003) The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 3(6):453–458

16. Friedl P, Alexander S (2011) Cancer invasion and the microenvi- ronment: plasticity and reciprocity. Cell 147(5):992–1009

17. Bernards R, Weinberg RA (2002) A progression puzzle. Nature 418(6900):823

18. Bozic I, Antal T, Ohtsuki H, Carter H, Kim D, Chen S, et al. (2010) Accumulation of driver and passenger mutations during tumor pro- gression. Proc Natl Acad Sci U S A 107:18545–18550

19. Pao W, Girard N (2011) New driver mutations in non-small-cell lung cancer. Lancet Oncol 12(2):175–180

20. Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, et al. (2013) Mutational landscape and significance across 12 major can- cer types. Nature 502:333–339

21. Sloan FA, Gelband H (2007) Cancer control in low- and middle- income countries. Institute of medicine (US) committee on cancer control in low- and middle-income countries national academies press (US), Washington DC http://wwwncbinlmnihgov/books/ NBK54030/. Accessed 23 February 2015

22. Hoffman MA, Ohh M, Yang H, Klco JM, Ivan M, Kaelin WG Jr (2001) Von Hippel-Lindau protein mutants linked to type 2C VHL disease preserve the ability to downregulate HIF. Hum Mol Genet 10(10):1019–1027

23. Park M, Lee S (2003) Cell Cycle and Cancer. J Biochem Mol Biol 36(1):60–65

24. Rivlin N, Brosh R, Oren M, Rotter V (2011) Mutations in the p53 tumor suppressor gene important milestones at the various steps of tumorigenesis. Genes Cancer 2(4):466–474

25. Knudson AG Jr (1971) Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A 68:820–823

26. Kufe DW, Pollock RE, Weichselbaum RR, et al (eds) (2003) Holland-Frei cancer medicine, 6th edn. BC Decker, Hamilton (ON) http://www.ncbi.nlm.nih.gov/books/NBK12354/. Accessed 24 February 2015

27. Boffetta P, Nyberg F (2003) Contribution of environmental factors to cancer risk. Br Med Bull 68:71–94

28. Yokota J (2000) Tumour progression and metastasis. Carcinogenesis 21(3):497–503

29. Doll R, Hill AB (1950) Smoking and carcinoma of the lung. Br Med J 2(4682):739–748

30. Carbone D (1992) Smoking and cancer. Am J Med 93(1):S13–S17

31. Heck DE, Vetrano AM, Mariano TM, Laskin JD (2003) UVB light stimulates production of reactive oxygen species: unexpected role for catalase. J Biol Chem 278(25):22432–22436

32. Hodis E, Watson IR, Kryukov GV, Arold ST, Imielinksi M, Theurillat J, et al. (2012) A Landscape of Driver Mutations in Melanoma. Cell 150(2):251–263

33. Moore PS, Chang Y (2010) Why do viruses cause cancer? Highlights of the first century of human tumour virology. Nat Rev Cancer 10(12):878–889

34. Talbot SJ, Crawford DH (2004) Viruses and tumours – an update. Eur J Cancer 40(13):1998–

2005

35. Polk D, Peek R (2010) Helicobacter pylori: gastric cancer and beyond. Nat Rev Cancer 10(6):403–414

36. Folkman J (2002) Role of Angiogenesis in tumor growth and Metastasis. Semin Oncol 29(6 Suppl 16):15–18

37. Ferrara N (2005) VEGF as a therapeutic target in cancer. Oncology 69(Suppl 3):11–16

38. Yang SR, Chida AS, Bauter MR, Shafiq N, Seweryniak K, Maggirwar SB, et al. (2006) Cigarette smoke induces proinflam- matory cytokine release by activation of NF-º B and posttransla- tional modifications of histone deacetylase in macrophages. Am J Physiol Lung Cell Mol Physiol 291(1):L46–L57

39. Karin M, Greten FR (2005) NF-º B: linking inflammation and im- munity to cancer development and progression. Nat Rev Immunol 5(10):749–759

40. Balkwill F (2006) TNF-± in promotion and progression of cancer. Cancer Metastasis Rev 25(4):409–416

41. Lee YS, Choi I, Ning Y, Kim NY, Khatchadourian V, Yang D, et al. (2012) Interleukin-8 and its receptor CXCR2 in the tumour micro- environment promote colon cancer growth, progression and metas- tasis. Br J Cancer 106(11):1833–1841

42. Han J, Haiman C, Niu T, Guo Q, Cox DG, Willett WC, et al. (2009) Genetic variation in DNA repair pathway genes and premenopausal breast cancer risk. Breast Cancer Res Treat 115(3):613–622

43. Traynor BJ, Singleton AB (2010) Nature versus Nurture: Death of a Dogma, and the Road Ahead. Neuron 68(2):196–200