Le cancer

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www.pneumocancero.com

Tumeur : bénin ou malin ?

- Une tumeur bénigne se distingue par son caractère limité (en général par une capsule conjonctive), par le fait qu'elle ne déforme pas l'organe d'origine, mais le repousse simplement ; elle n'envahit pas les organes de voisinage et ne donne pas de métastases à distance.
- La tumeur maligne, au contraire, est mal limitée, bouleverse la structure normale de l'organe, envahit les structures de voisinage. Par ailleurs, elle entraîne des métastases par voie lymphatique (métastases ganglionnaires) et par voie sanguine (métastases viscérales).
- Le caractère de bénignité ou de malignité est donc affirmé par la conjonction de critères cliniques et anatomopathologiques. Néanmoins, c'est l'anatomopathologie qui permet seule d'affirmer qu'une tumeur est maligne. Le cancer est une maladie cellulaire.

Tableau 1 Principales caractéristiques des méthodes diagnostiques et exemples d'utilisation

Caractères histologiques de malignité

- macroscopiquement : tumeur irrégulière, envahissant les organes de voisinage
- microscopiquement :
  - → noyaux irréguliers, indice mitotique élevé
  - → désorganisation structurale
  - → néovascularisation anarchique

Caractères cytologiques de malignité

- gros noyau irrégulier
- chromatine dense
- mitoses anormales

Immuno-histochimie (anticorps monoclonaux marqués par fluorescence ou immunopéroxydase)

Exemple :

- caractérisation des cellules sanguines et ganglionnaires (CD20 pour les lymphomes B)
- récepteurs hormonaux dans le cancer du sein
- récepteur erbB2 dans le cancer du sein
- phosphatase alcaline placentaire dans les tumeurs germinales
- Ki67 comme indice mitotique

Techniques de cytogénétique et biologie moléculaire

Exemple :

- translocation 9-22 dans la leucémie myéloïde chronique
- transcrit 11-22 dans le sarcome d'Ewing

Les théories

Comment se développe le cancer?

Les théories

- Théorie réductionniste (mutations moléculaires)
- Théorie du champ d'organisation tissulaire (holisme)
- Théorie de l'ontophylogenèse (réconciliation)

Théorie réductionniste (modèle des mutations)

- 1960 : chromosome Philadelphie = translocation chromosomique réciproque entre les chromosomes 9 et 22 (leucémie myéloïde chronique)
- Paradigme oncogénique : une cellule, par étapes successives d'anomalies génétiques somatiques, attrape un avantage compétitif croissant par rapport aux cellules normales voisines

Fig. 1. Model of clonal evolution in neoplasia. Carcinogen-induced change in progenitor normal cell (N) produces a diploid tumor cell (T_1, 46 chromosomes) with growth advantage permitting clonal expansion to begin. Genetic instability of T_1 cells leads to production of variants (illustrated by changes in chromosome number, T_2 to T_6). Most variants die, due to metabolic or immunologic disadvantage (hatched circles); occasionally one has an additional selective advantage (for example, T_2, 47 chromosomes), and its progeny become the predominant subpopulation until an even more favorable variant appears (for example, T_4). The stepwise sequence in each tumor differs (being partially determined by environmental pressures on selection), and results in a different, aneuploid karyotype in each fully developed malignancy (T_6). Biological characteristics of tumor progression (for example, morphological and metabolic loss of differentiation, invasion and metastasis, resistance to therapy) parallel the stages of genetic evolution. Human tumors with minimal chromosome change (diploid acute leukemia, chronic granulocytic leukemia) are considered to be early in clonal evolution; human solid cancers, typically highly aneuploid, are viewed as late in the developmental process.

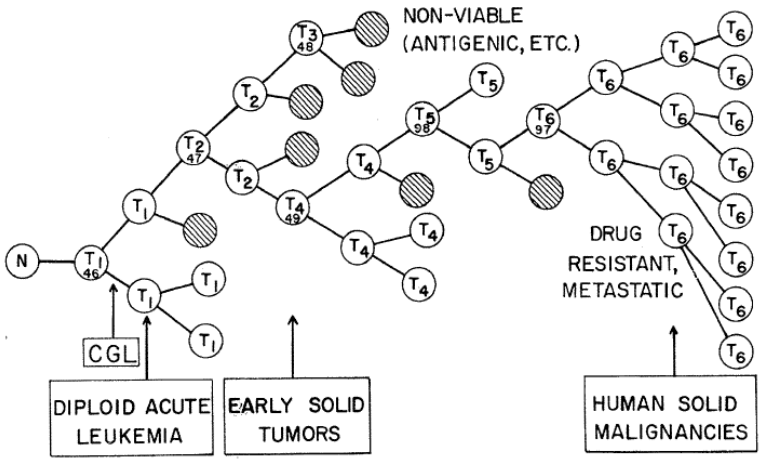

Table 1. The birth of the oncogene paradigm.

1911	Discovery by P. Rous of the first cancer virus
1961	Models of gene regulation (F. Jacob and J. Monod)
1969	The Provirus Model (R. J. Huebner and G. J. Todaro)
1976	Discovery of the first cellular oncogene, homologons to a retroural oncogene (D. Stehelin, H. Varmus, M. Bishop)
1979–1980	Intercellular passage of the transformed phenotype by a single gene transfer (G. Cooper, R. Weinberg)
1982	Transformation may result from a point mutation in a cellular oncogene
1983–1984	Oncogenes code for growth factors or growth-factor receptors
1986	Discovery of the first antioncogene (tumor suppressor gene)

Journal of the History of Biology **30:** 1–29, 1997.

un gène muté unique a été déclaré comme suffisant pour générer une tumeur

Proc. Natl. Acad. Sci. USA
Vol. 76, No. 11, pp. 5714–5718, November 1979
Cell Biology

Passage of phenotypes of chemically transformed cells via transfection of DNA and chromatin

(chemical carcinogenesis/transformation alleles/Southern blotting)

CHIAHO SHIH, BEN-ZION SHILO, MITCHELL P. GOLDFARB, ANN DANNENBERG, AND ROBERT A. WEINBERG

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Les oncogènes

Ann. Rev. Biochem. 1983. 52:301–54

CELLULAR ONCOGENES AND RETROVIRUSES

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Table 1 Oncogenes transduced by retroviruses

Viral oncogene[a]	Species of origin	Tumorigenicity	Protein products	
			Biochemical function	Subcellular location
v-*src*	Chicken	Sarsoma	PK(tyr)[b]	Plasma membrane
v-*fps*/v-*fes*	Chicken and cat	Sarcoma	PK(tyr)	Plasma membrane
v-*yes*	Chicken	Sarcoma	PK(tyr)	?[d]
v-*ros*	Chicken	Sarcoma	PK(tyr)	?
v-*ski*	Chicken		?	?
v-*myc*	Chicken	Carcinoma, sarcoma and myelocytoma	DNA binding	Nucleus
v-*erb*-A	Chicken	?	?	Cytoplasm
v-*erb*-B	Chicken	Erythroleukemia and sarcoma	?	Membranes
v-*myb*	Chicken	Myeloblastic leukemia	?	Nucleus
v-*rel*	Turkey	Lymphatic leukemia	?	?
v-*mos*	Mouse	Sarcoma	?	Cytoplasm
v-*abl*	Mouse and cat	B-cell lymphoma	PK(tyr)	Plasma membrane
v-*fos*	Mouse	Sarcoma	?	?
v-Ha-*ras*/ v-*bas*[c, e]	Rat and mouse	Sarcoma and erythroleukemia	Binds GTP; PK(thr)[f]	Plasma membrane
v-Ki-*ras*[e]	Rat	Sarcoma and erythroleukemia	Binds GTP; PK(thr)[f]	Plasma membrane
v-*fms*	Cat	Sarcoma	?	Membranes
v-*sis*	Woolly monkey and cat	Sarcoma	?	?

Table 2 Proteins encoded by cellular oncogenes

Oncogene	Protein[a]	Alleged function	
		Cellular gene	Viral cognate
c-*src*	60*K*	tyr kinase[b]	tyr kinase[c]
c-*fps*	98*K*	tyr kinase	tyr kinase
c-*abl*	150*K*	?	tyr kinase
c-*ras* (Ha/Ki)	21*K*	thr kinase[c]	thr kinase[c]
c-*fes*	92*K*	?	tyr kinase

[a] Products of c-*onc*'s were identified by using antisera prepared originally against proteins encoded by the cognate v-*onc*'s. In two instances (*src* and *ras*), the proteins encoded by the viral and cellular genes have virtually identical sizes. Otherwise, the cellular proteins have molecular weights appreciably different from those of the viral proteins because the coding regions in the v-*onc*'s include substantial proteins of viral structural genes.

[b] Tyrosine-specific protein kinase activity was identified by phosphotransfer in immunoprecipitates (100, 102).

[c] The products of v-*ras* and c-*ras* have a selective kinase activity that phosphorylates threonine in the products of the oncogenes themselves, but in no other protein substrate tested to date.

Table 1. Different influences on tumor cell evolution.

Factors influencing different stages	Stages of tumor development		
	Initiation of neoplasia	Genetic instability	Emergence of variant subpopulations
	Carcinogens (12)		
Radiation	+	+	
Chemicals	+		
Viruses	+	+	
	Gene defects		
Inherited (*17, 35*)			
Increased mutability (chromosome breakage, and other)	+	+	
Immunodeficiency			+
Undefined	+		
Acquired (*36*)			
Increased mutability (nondisjunction, and other)		+	
	Tumor environment (31, 40)		
Nutrition		+	+
Infection			+
Immune status of patient (*41*)			+
Therapy		+	+

*A plus sign denotes those stages of tumor evolution influenced by the factor indicated. See the text for details.

Weinberg

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The Hallmarks of Cancer

Review

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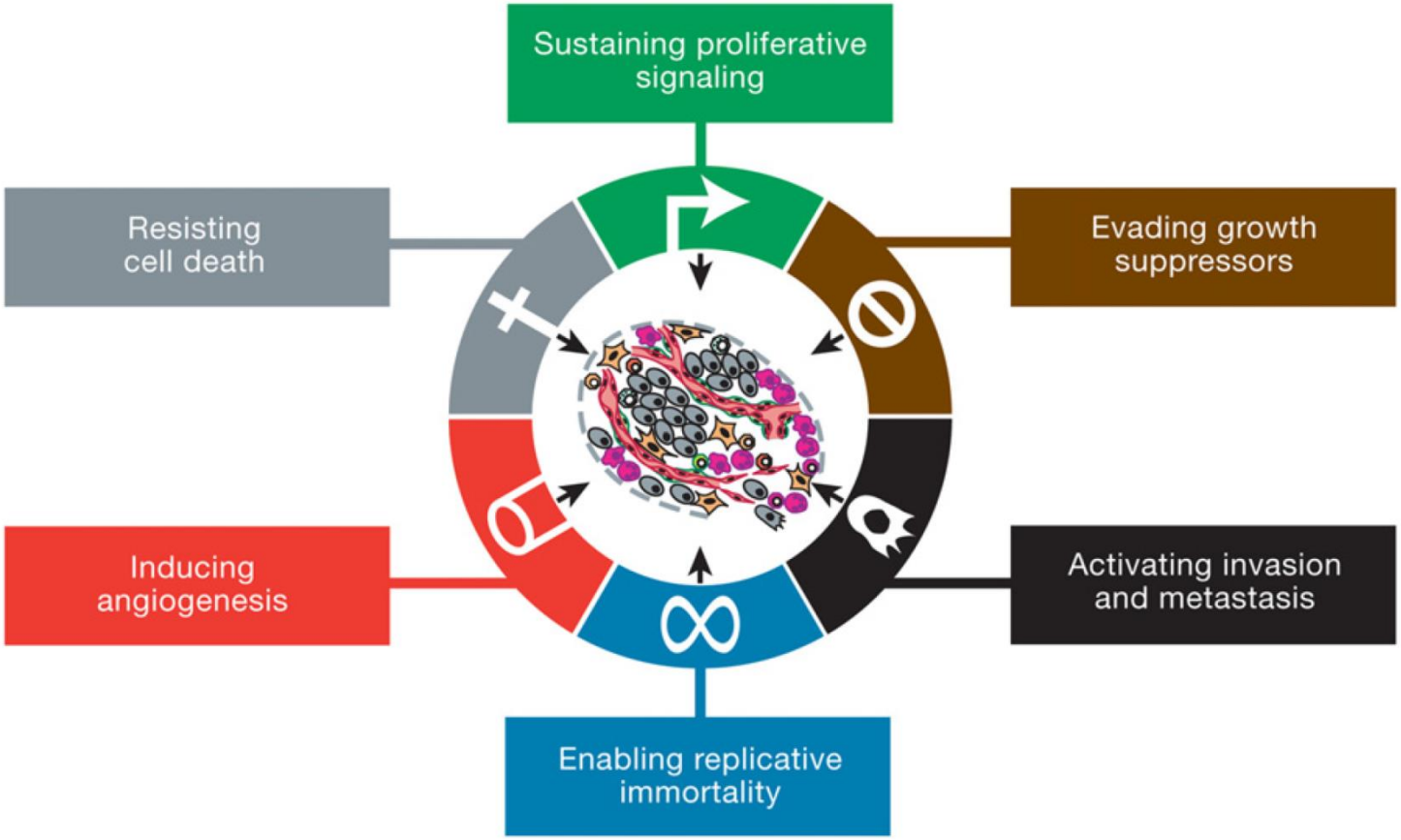
evolve progressively from normalcy via a series of premalignant states into invasive cancers (Foulds, 1954).

These observations have been rendered more concrete by a large body of work indicating that the genomes of tumor cells are invariably altered at multiple sites, having suffered disruption through lesions as subtle as point mutations and as obvious as changes in chromosome complement (e.g., Kinzler and Vogelstein, 1996). Transformation of cultured cells is itself a multistep process: rodent cells require at least two intra

The Hallmarks of Cancer



Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

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Propriétés de la cellule transformée

- activation constitutive de signaux de prolifération
- neutralisation de régulateurs négatifs du cycle cellulaire
- perte de sensibilité aux signaux de mort
- modifications du métabolisme énergétique
- instabilité génétique
- capacité à promouvoir une néoangiogenèse ou une réaction inflammatoire
- acquisition d'un métabolisme spécifique
- échappement à la réponse immunitaire

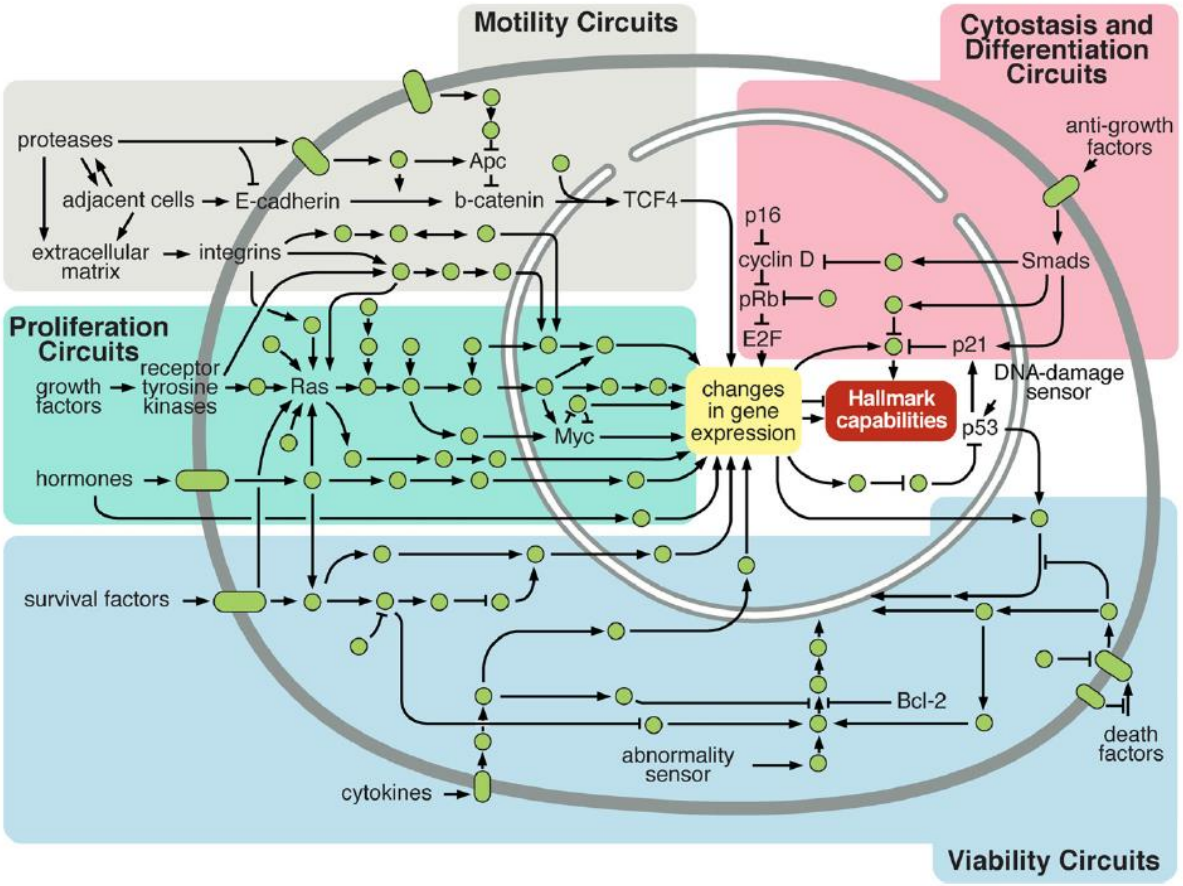

Figure 2. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell

An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate subcircuits, depicted here in differently colored fields, are specialized to orchestrate the various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such subcircuits. In addition, because each cancer cell is exposed to a complex mixture of signals from its microenvironment, each of these subcircuits is connected with signals originating from other cells in the tumor microenvironment, as outlined in Figure 5.

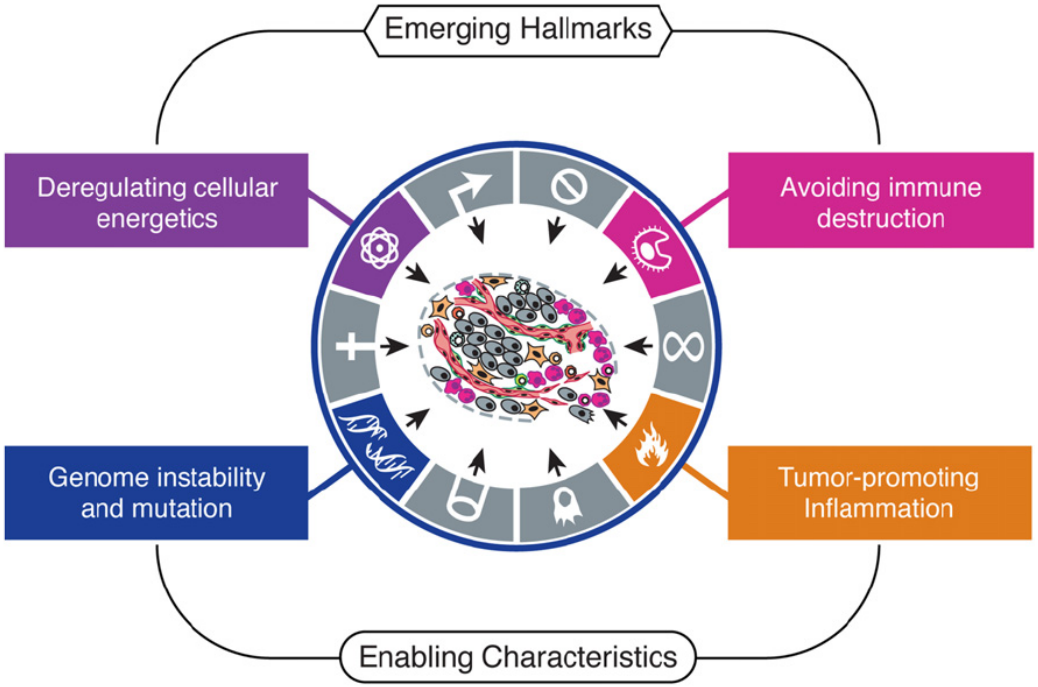

Figure 3. Emerging Hallmarks and Enabling Characteristics

An increasing body of research suggests that two additional hallmarks of cancer are involved in the pathogenesis of some and perhaps all cancers. One involves the capability to modify, or reprogram, cellular metabolism in order to most effectively support neoplastic proliferation. The second allows cancer cells to evade immunological destruction, in particular by T and B lymphocytes, macrophages, and natural killer cells. Because neither capability is yet generalized and fully validated, they are labeled as emerging hallmarks. Additionally, two consequential characteristics of neoplasia facilitate acquisition of both core and emerging hallmarks. Genomic instability and thus mutability endow cancer cells with genetic alterations that drive tumor progression. Inflammation by innate immune cells designed to fight infections and heal wounds can instead result in their inadvertent support of multiple hallmark capabilities, thereby manifesting the now widely appreciated tumor-promoting consequences of inflammatory responses.

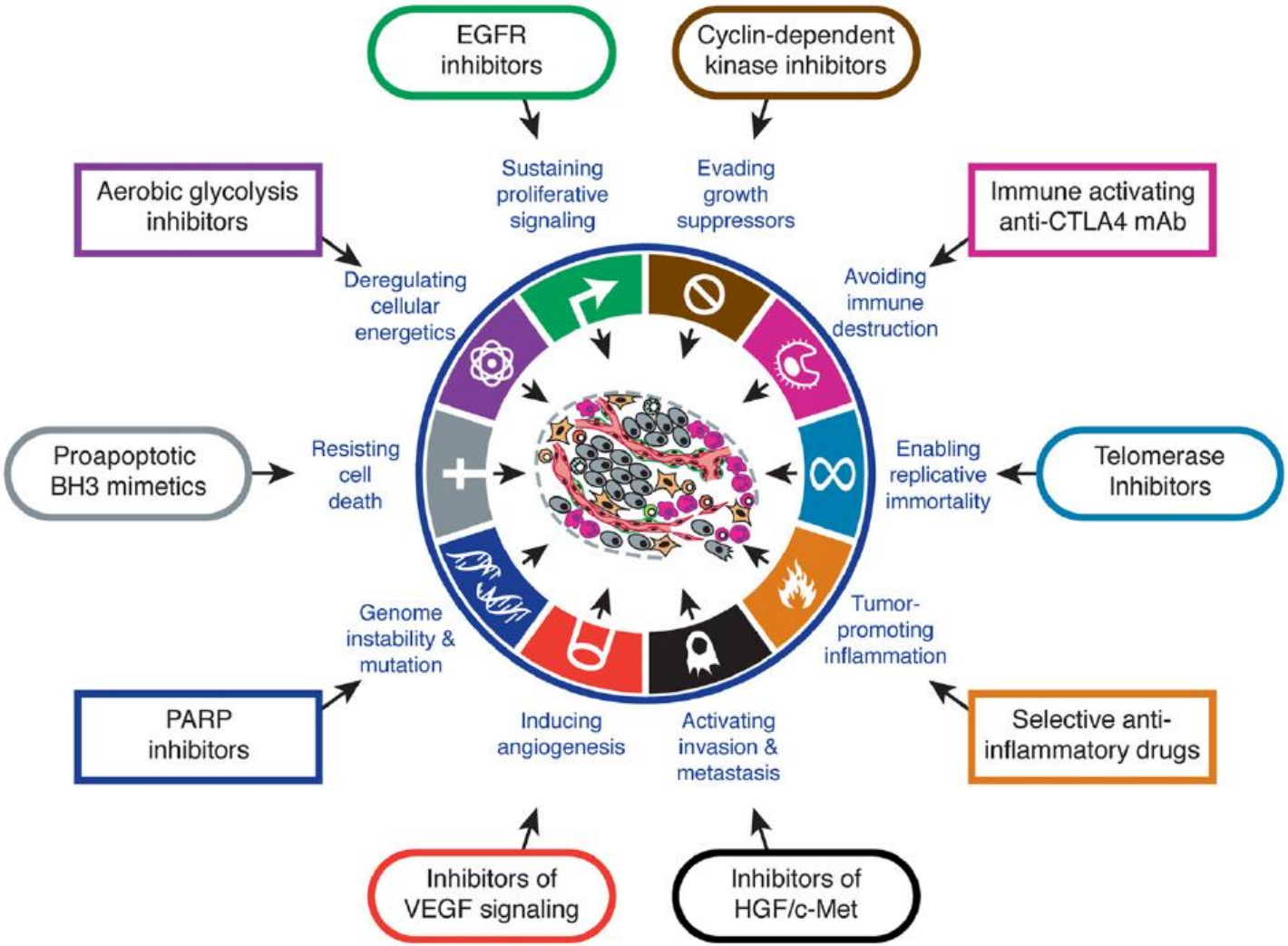

Figure 6. Therapeutic Targeting of the Hallmarks of Cancer

Drugs that interfere with each of the acquired capabilities necessary for tumor growth and progression have been developed and are in clinical trials or in some cases approved for clinical use in treating certain forms of human cancer. Additionally, the investigational drugs are being developed to target each of the enabling characteristics and emerging hallmarks depicted in Figure 3, which also hold promise as cancer therapeutics. The drugs listed are but illustrative examples; there is a deep pipeline of candidate drugs with different molecular targets and modes of action in development for most of these hallmarks.

Conséquence de la théorie

= Approche ciblée sur les anomalies génétiques

Grande hétérogénéité des anomalies génomiques

- Simples :
  - mutations
  - délétions
  - translocation
- Complexes :
  - perte de fragments chromosomiques ou de chromosomes entiers
  - perte d'hétérozygotie sur de larges fragments du génome
  - tempête mutationnelle au voisinage d'un réarrangement chromosomique
  - cassures chromosomiques brutales suivies d'un réarrangement aléatoire des fragments (*chromotripsis*)

Conséquences des altérations génétiques

- Neutres
- Délétères
- Drivers (motrices)
  - Épistasie : une mutation, neutre lorsque le reste du génome est normal, peut devenir *driver* lorsqu'elle survient dans le contexte de l'altération d'un ou plusieurs autres gènes

Accumulation of driver and passenger mutations during tumor progression

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Contributed by Bert Vogelstein, August 11, 2010 (sent for review May 26, 2010)

Major efforts to sequence cancer genomes are now occurring throughout the world. Though the emerging data from these studies are illuminating, their reconciliation with epidemiologic and clinical observations poses a major challenge. In the current study, we provide a mathematical model that begins to address this challenge. We model tumors as a discrete time branching process that starts with a single driver mutation and proceeds as each new driver mutation leads to a slightly increased rate of clonal expansion. Using the model, we observe tremendous variation in the rate of tumor development—providing an understanding of the heterogeneity in tumor sizes and development times that have been observed by epidemiologists and clinicians. Furthermore, the model provides a simple formula for the number of driver mutations as a function of the total number of mutations in the tumor. Finally, when applied to recent experimental data, the model allows us to calculate the actual selective advantage provided by typical somatic mutations in human tumors in situ. This selective advantage is surprisingly small—0.004 ± 0.0004—and has major implications for experimental cancer research.

line of investigation which has just recently been initiated (22, 23). In the model presented in this paper, we assume that each new driver mutation leads to a slightly faster tumor growth rate. This model is as simple as possible, because the analytical results depend on only three parameters: the average driver mutation rate u, the average selective advantage associated with driver mutations s, and the average cell division time T.

Tumors are initiated by the first genetic alteration that provides a relative fitness advantage. In the case of many leukemias, this would represent the first alteration of an oncogene, such as a translocation between *BCR* (breakpoint cluster region gene) and *ABL* (V-abl Abelson murine leukemia viral oncogene homolog 1 gene). In the case of solid tumors, the mutation that initiated the process might actually be the second "hit" in a tumor suppressor gene—the first hit affects one allele, without causing a growth change, whereas the second hit, in the opposite allele, leaves the cell without any functional suppressor, in accord with the two-hit hypothesis (24). It is important to point out that we are modeling tumor progression, not initiation (14, 15), because

Les séquençages complets

ARTICLE

doi:10.1038/nature12912

Discovery and saturation analysis of cancer genes across 21 tumour types

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Although a few cancer genes are mutated in a high proportion of tumours of a given type (>20%), most are mutated at intermediate frequencies (2–20%). To explore the feasibility of creating a comprehensive catalogue of cancer genes, we analysed somatic point mutations in exome sequences from 4,742 human cancers and their matched normal-tissue samples across 21 cancer types. We found that large-scale genomic analysis can identify nearly all known cancer genes in these tumour types. Our analysis also identified 33 genes that were not previously known to be significantly mutated in cancer, including genes related to proliferation, apoptosis, genome stability, chromatin regulation, immune evasion, RNA processing and protein homeostasis. Down-sampling analysis indicates that larger sample sizes will reveal many more genes mutated at clinically important frequencies. We estimate that near-saturation may be achieved with 600–5,000 samples per tumour type, depending on background mutation frequency. The results may help to guide the next stage of cancer genomics.

Table 1 | List of the 21 tumour types analysed

Tumour type	No. of tumour–normal pairs	Median somatic mutation frequency (per Mb)	No. of significantly mutated genes	No. of additional significant genes found under RHT
Acute myeloid leukaemia	196	0.4	26	1
Bladder	99	7.1	24	10
Breast	892	1.2	32	5
Carcinoid	54	0.5	1	0
Chronic lymphocytic leukaemia	159	0.6	7	8
Colorectal	233	3.1	23	12
Diffuse large B-cell lymphoma	58	3.3	16	7
Endometrial	248	2.5	58	15
Oesophageal adenocarcinoma	141	4.0	8	7
Glioblastoma multiforme	291	2.2	22	4
Head and neck	384	3.9	25	9
Kidney clear cell	417	1.9	15	6
Lung adenocarcinoma	405	8.1	22	10
Lung squamous cell carcinoma	178	9.9	11	13
Medulloblastoma	92	0.3	2	1
Melanoma	118	12.9	19	9
Multiple myeloma	207	1.6	11	3
Neuroblastoma	81	0.5	1	0
Ovarian	316	1.7	5	5
Prostate	138	0.7	4	2
Rhabdoid tumour	35	0.1	1	0

The number of significantly mutated genes detected using the MutSig suite when analysing the full set of genes. RHT, restricted hypothesis testing on the set of cancer genes found in all the other tumour types. Supplementary Table 3 lists the cancer genes found in each tumour type and their frequencies (per cent of patients with mutations).

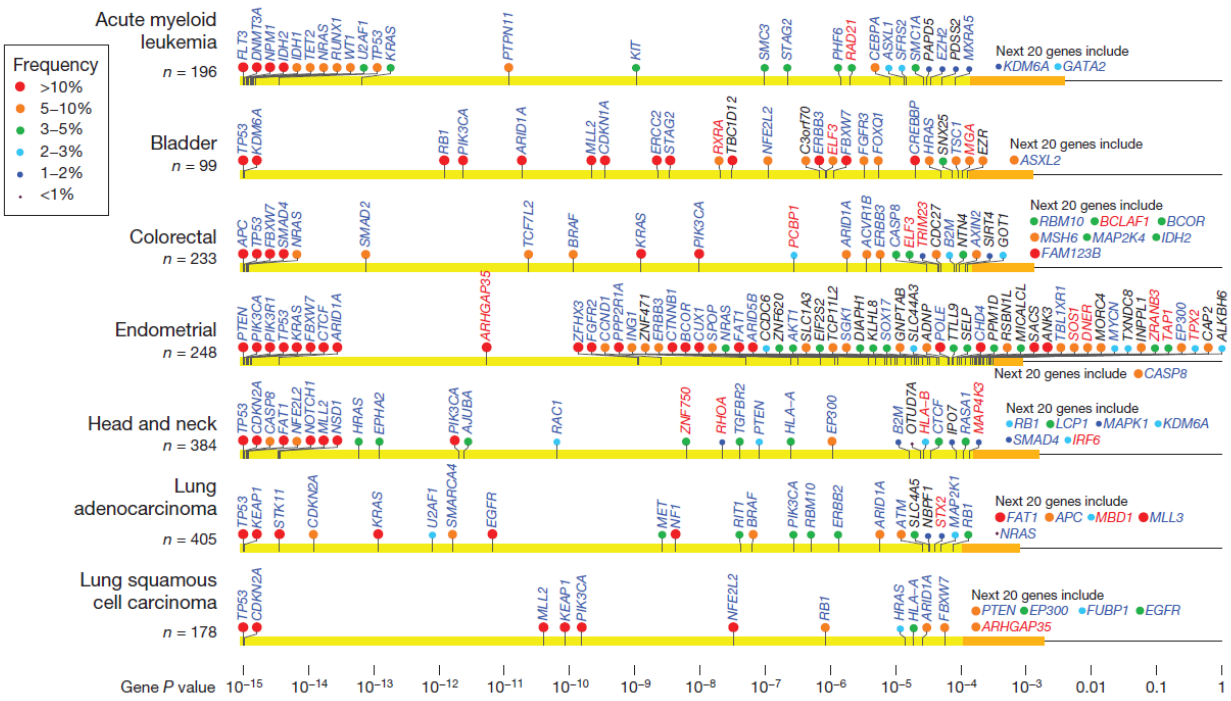
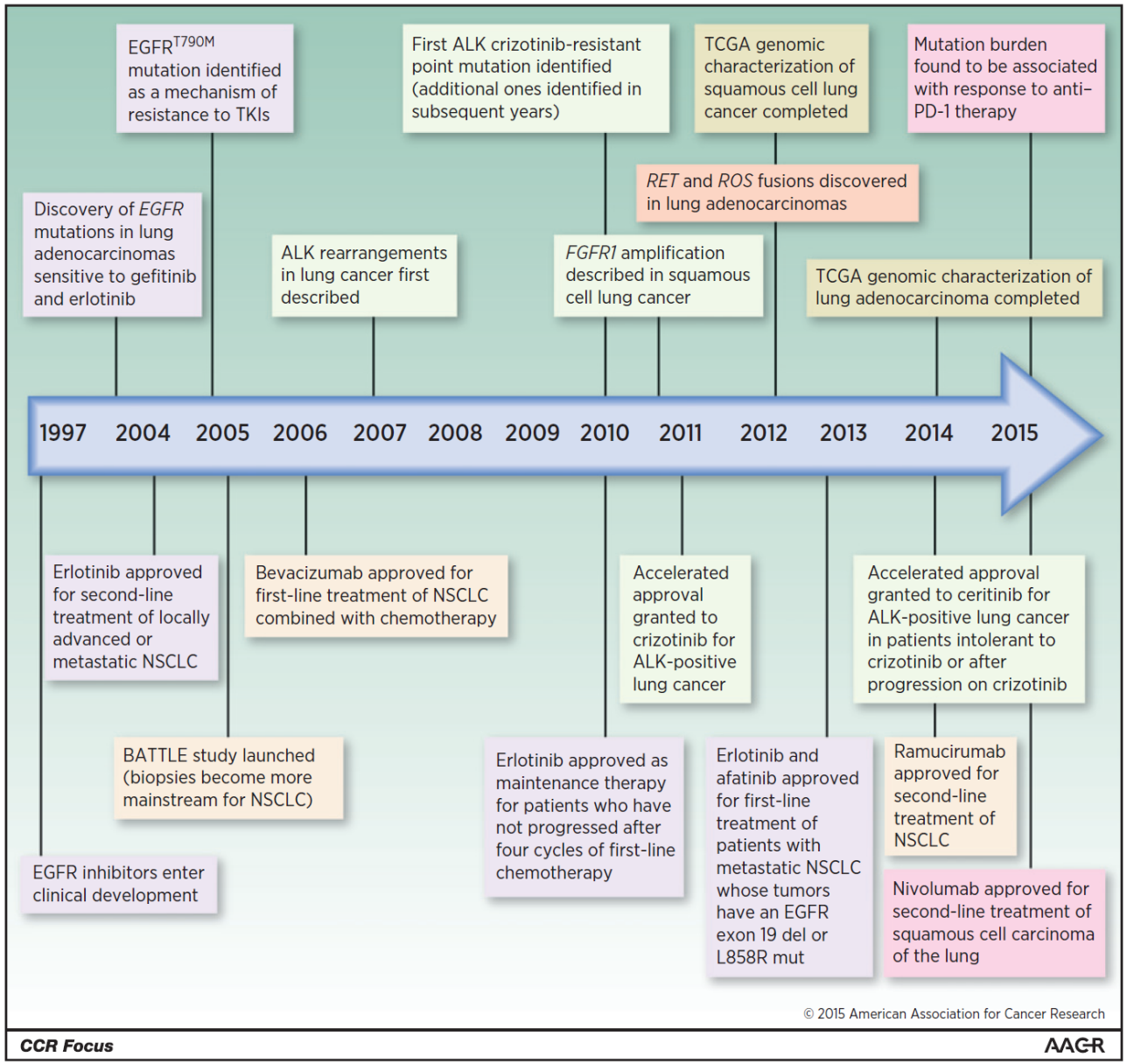


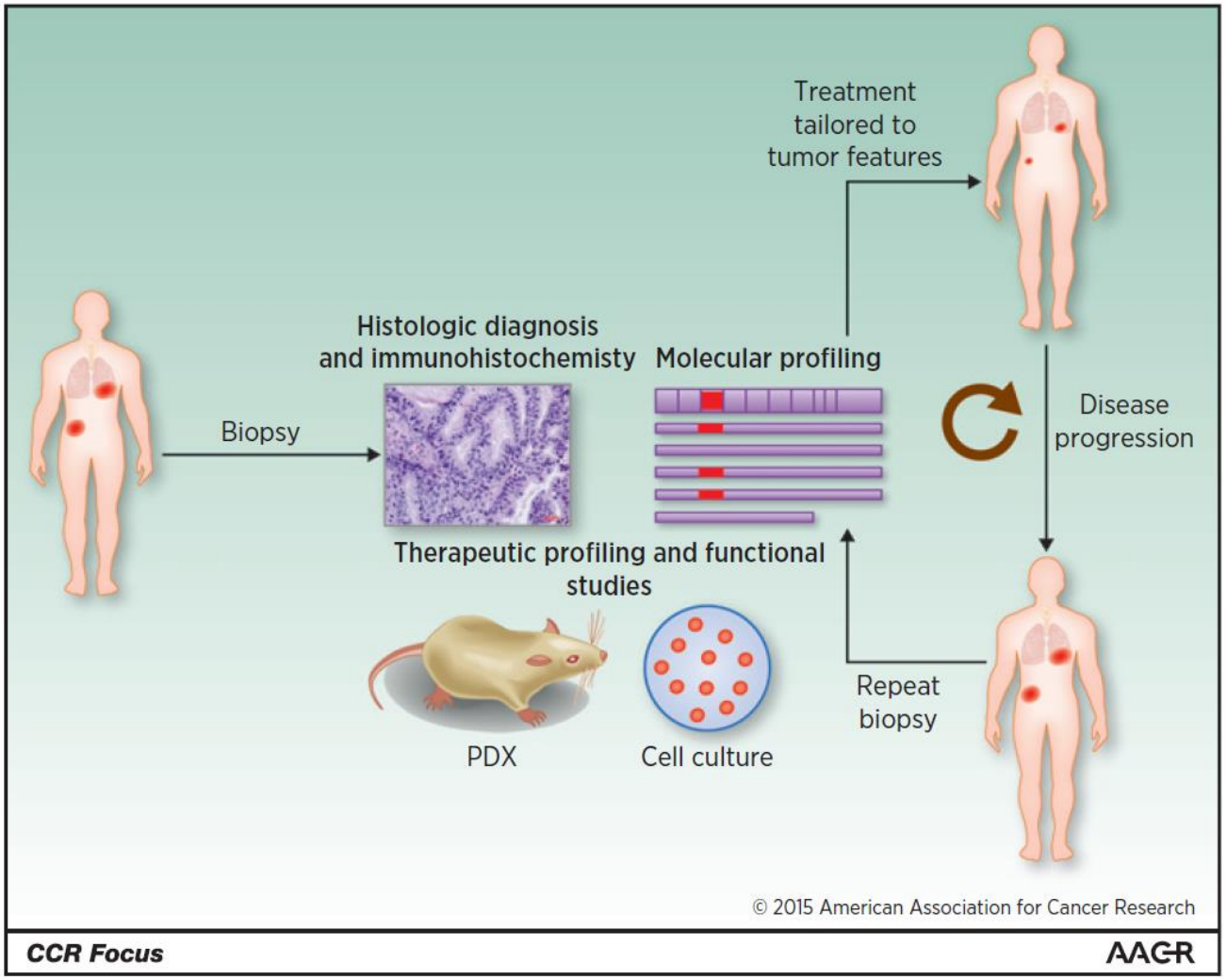
Figure 2 | Cancer genes in selected tumour types. Genes are arranged on the horizontal line according to *P* value (combined value for the three tests in MutSig). Yellow region contains genes that achieve FDR $q \leq 0.1$. Orange interval contains *P* values for the next 20 genes. Gene-name colour indicates whether the gene is a known cancer gene (blue), a novel gene with clear connection to cancer (red, discussed in text), or an additional novel gene (black). Circle colour indicates the frequency (percentage of patients carrying non-silent somatic mutations) in that tumour type; see also Supplementary Fig. 5.

Conséquences

- Développement d'une médecine thérapeutique de précision



Clin Cancer Res; 21(10); 2213–20. ©2015 AACR.


Treatment
tailored to
tumor features
Histologic diagnosis
and immunohistochemisty
Molecular profiling
Biopsy
Disease
progression
Therapeutic profiling and functional
studies
Repeat
biopsy
PDX
Cell culture
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Raisons de l'échec des traitements

Lié à l'hétérogénéité intratumorale

- Par sélection des clones les plus agressifs et les plus résistants
- Par expansion de multiples sous-clones perturbant l'équilibre interne d'une tumeur dans laquelle les clones les moins agressifs contrôlaient la croissance de clones plus agressifs
- Par des paramètres environnementaux comme la localisation de cellules dans des zones d'hypoxie faiblement vascularisés
- Par des paramètres liés à la cellule d'origine, tels que la résistance intrinsèque des cellules souches d'un tissu
- Par des facteurs épigénétiques
- Par la mise en quiescence de certaines cellules du clone.

Mais

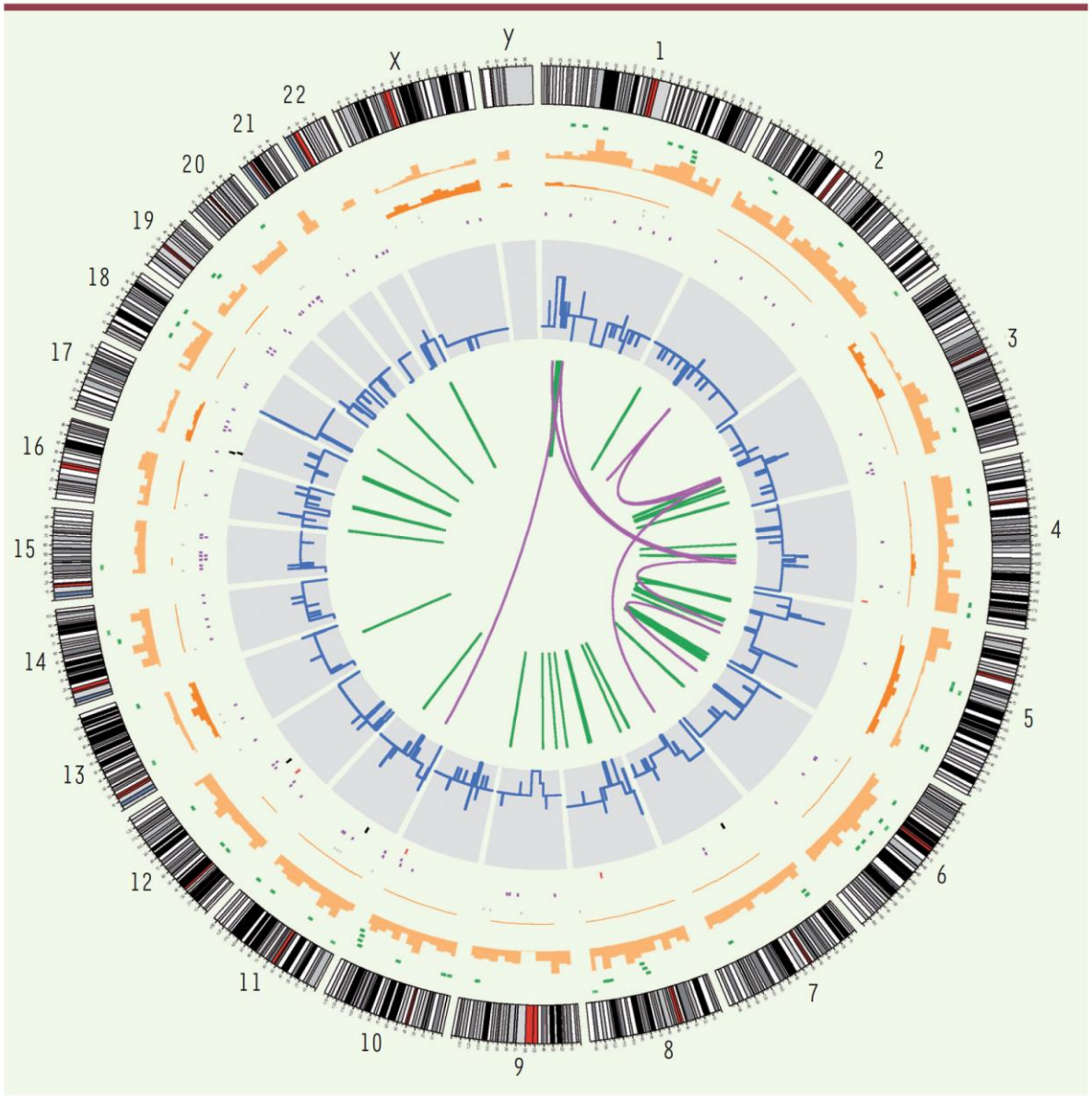

Figure 2. ***L'extrême variété des changements observés dans l'ADN d'un cancer du poumon (par rapport au tissu normal).*** Les chromosomes sont figurés à la périphérie du cercle. En allant vers l'intérieur, on trouve les insertions (vert clair), les délétions (vert foncé), les substitutions hétérozygotes (orange clair) et homozygotes (orange foncé) repérées par leur densité par intervalle de dix mégabases, les substitutions dans des régions codantes : silencieuses (gris), faux-sens (pourpre), nonsens (rouge) et dans les sites d'épissage (noir). Les variations de nombre de copies sont indiquées en bleu, les zones de perte d'hétérozygotie en rouge, les réarrangements intra-chromosomiques en vert et inter-chromosomiques en pourpre (figure aimablement donnée par Peter Campbell, *Wellcome Trust Sanger Institute*).

- un nombre élevé de mutations est généralement observé (de quelques centaines à quelques dizaines de milliers de mutations) mais celles qui affectent la séquence des protéines sont beaucoup moins nombreuses
- forte hétérogénéité intertumorale
- Dans une même tumeur : sous-populations distinctes avec des profils génétiques complexes, sans sous-population intermédiaire, ni événement génétique initial

- les mutations des cellules cancéreuses ont été arbitrairement classées comme putativement causales (mutations *drivers* ou conductrices) et comme non pertinentes (mutations *passengers*)
- inférences non vérifiables, étant donné qu'il s'agissait de cancers déjà développés

- Des mutations somatiques (silencieuses) ont été identifiées dans les cellules des tissus normaux
- Une étude n'a identifié aucune mutation somatique dans un certain type de tumeurs humaines, les épendymomes

ARTICLE

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Epigenomic alterations define lethal CIMP-positive ependymomas of infancy

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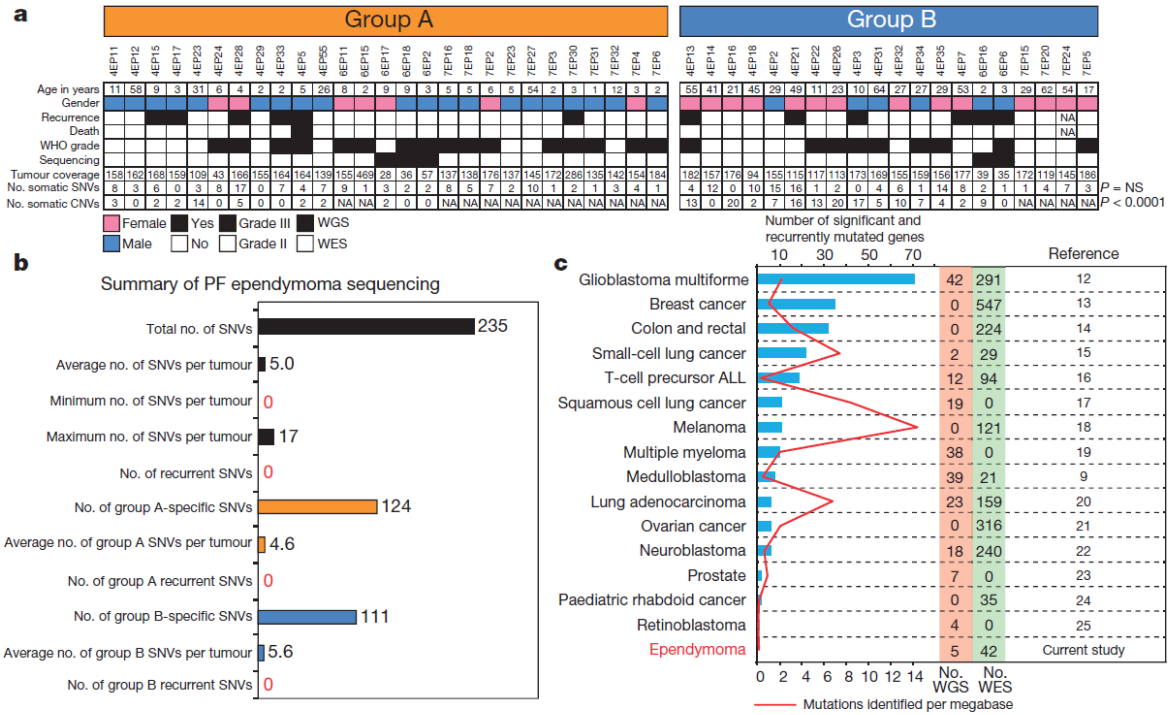

Figure 1 | Somatic SNVs are rare in the posterior fossa ependymoma genome. **a**, Summary of clinical and genomic details of PF ependymomas stratified according to group A and group B ependymoma (Wilcoxon rank-sum test). CNV, copy number variation; NA, not available; NS, not significant; WES, whole-exome sequencing; WGS, whole-genome sequencing. **b**, Bar graphs summarizing the numbers and frequencies of SNVs detected by whole-genome and whole-exome sequencing of PF ependymomas. **c**, Comparison of numbers of significant and recurrently mutated genes, and mutation rates, in several whole-genome and whole-exome sequencing studies of adult and paediatric cancers (false discovery rate (FDR) < 0.1).

Paradoxe de Peto

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Research

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Solutions to Peto's paradox revealed by mathematical modelling and cross-species cancer gene analysis

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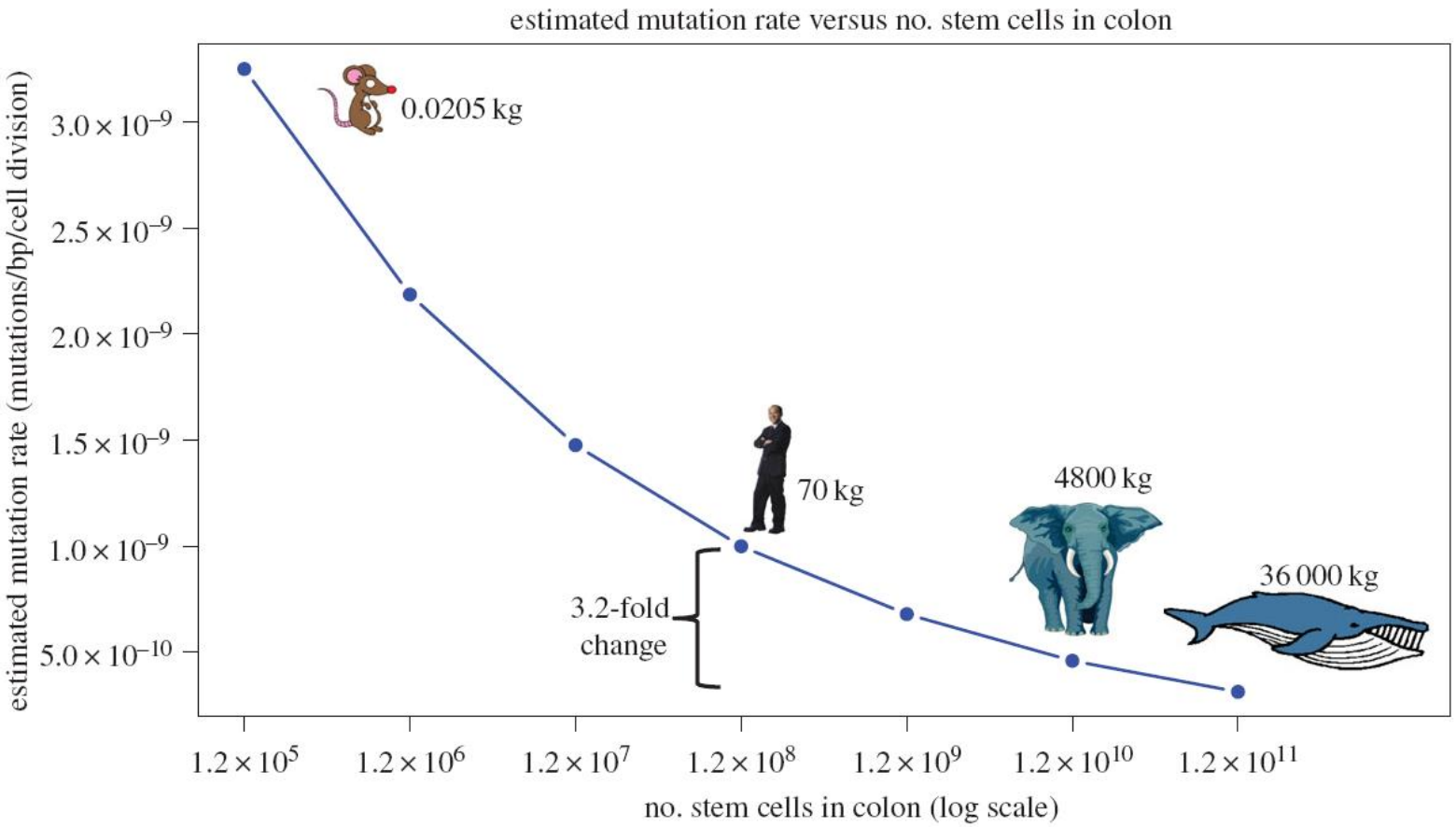
Whales have 1000-fold more cells than humans and mice have 1000-fold fewer; however, cancer risk across species does not increase with the number of somatic cells and the lifespan of the organism. This observation


estimated mutation rate versus no. stem cells in colon
estimated mutation rate (mutations/bp/cell division)
3.0 × 10−9
2.5 × 10−9
2.0 × 10−9
1.5 × 10−9
1.0 × 10−9
5.0 × 10−10
0.0205 kg
70 kg
4800 kg
36 000 kg
3.2-fold change
1.2 × 10^5
1.2 × 10^6
1.2 × 10^7
1.2 × 10^8
1.2 × 10^9
1.2 × 10^10
1.2 × 10^11
no. stem cells in colon (log scale)

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Variation in cancer risk among tissues can be explained by the number of stem cell divisions

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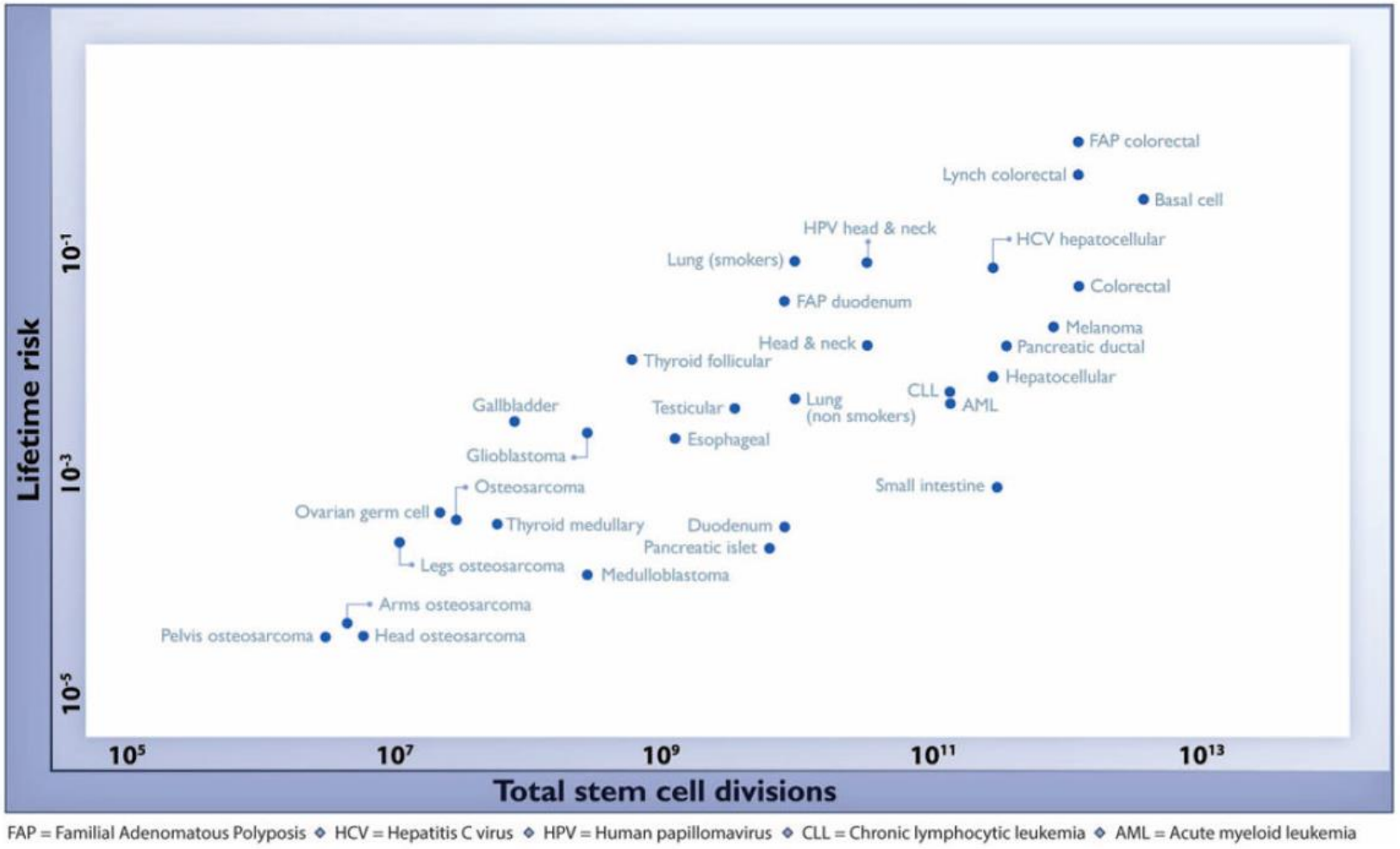

Fig. 1. The relationship between the number of stem cell divisions in the lifetime of a given tissue and the lifetime risk of cancer in that tissue

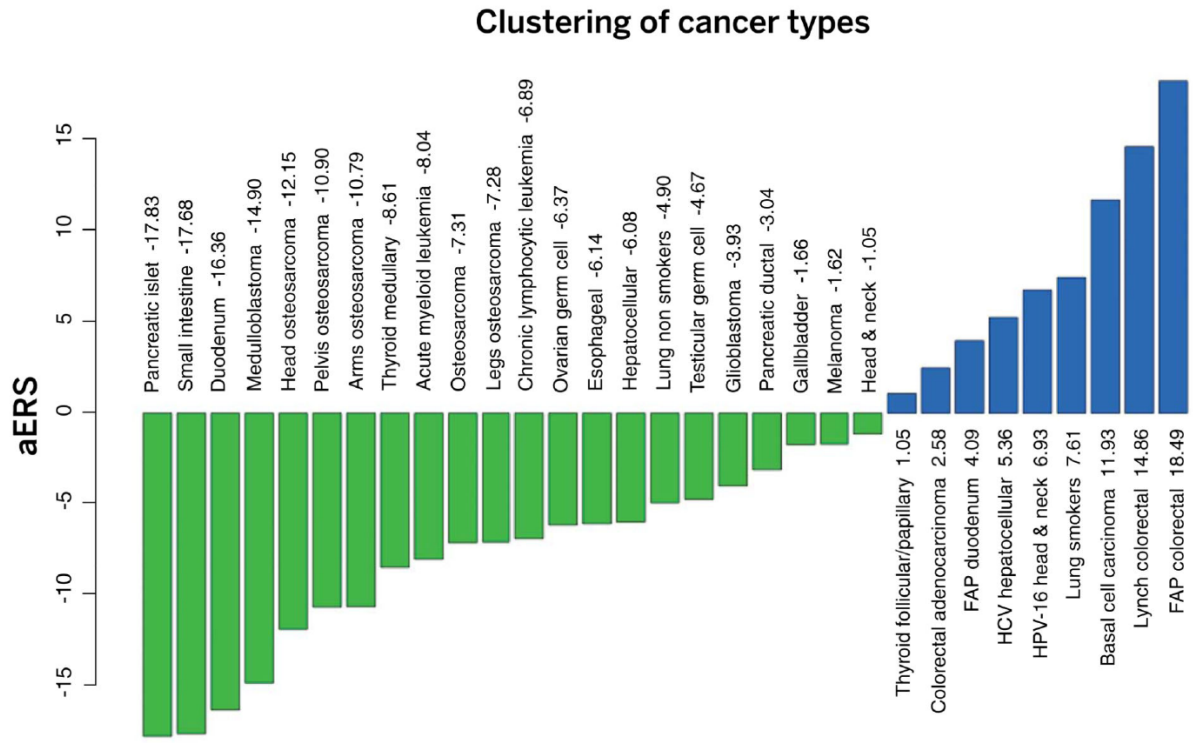

Fig. 2. Stochastic (replicative) factors versus environmental and inherited factors: R-tumor versus D-tumor classification

The adjusted ERS (aERS) is indicated next to the name of each cancer type. R-tumors (green) have negative aERS and appear to be mainly due to stochastic effects associated with DNA replication of the tissues' stem cells, whereas D-tumors (blue) have positive aERS. Importantly, although the aERS was calculated without any knowledge of the influence of environmental or inherited factors, tumors with high aERS proved to be precisely those known to be associated with these factors. For details of the derivation of aERS, see the supplementary materials.

ERS = extrarisk factors

Théorie du champ d'organisation tissulaire (holisme ou auto-organisation)

- Au niveau organisme, s'appuie sur la biologie des systèmes
- Pour le holisme, c'est le niveau supérieur (le tout) qui impose l'ordre aux autres niveaux, alors que pour le réductionnisme, c'est le niveau inférieur qui propage ses effets organisateurs aux niveaux supérieurs.
- Accepte le rôle du hasard en utilisant des notions de bruit, de fluctuations aléatoires, d'incertitude

champ d'organisation tissulaire

Le cancer est une maladie des tissus où les cancérigènes (directement) et les mutations dans la lignée germinale (indirectement) peuvent altérer les interactions normales entre le stroma et l'épithélium adjacent

- Les agents cancérigènes génèrent une perturbation dans les interactions entre cellules qui maintiennent l'organisation cellulaire, la réparation des tissus et l'homéostasie locale
- Cette architecture altérée permet aux cellules des tumeurs d'exprimer leur état par défaut, c'est-à-dire **la prolifération et la motilité** (en formant les métastases). Ce qui se produit au sein des cellules individuelles de la tumeur est donc une conséquence, et non une cause, de cette communication altérée entre les tissus.
- Les mutations représentent un épiphénomène non pertinent du point de vue de la cancérogenèse et de sa progression

le cancer est un développement qui a mal tourné

- les programmes génétiques sont modulés par l'environnement
- l'organicisme voit les embryons comme des systèmes dynamiques ouverts, où l'on retrouve des causalités multiples, ascendantes, descendantes et transversales
- la théorie du champ d'organisation tissulaire situe plutôt la cancérogenèse au niveau tissulaire (et non cellulaire) de l'organisation biologique
- l'architecture altérée des tissus rend possible l'expression de l'état par défaut, et donc la croissance tumorale et les métastases

Arguments cancer conséquence secondaire des altérations tissulaires

Désorganisation tissulaire: observée dans certaines maladies chroniques et qui précède souvent la formation de tumeurs épithéliales

- maladies chroniques du foie (hépatites C et B, cirrhose alcoolique, hémochromatose, etc.)
- maladies chroniques du poumon (bronchite chronique, emphysème, asthme, infection pulmonaire chronique, fibrose pulmonaire primaire)

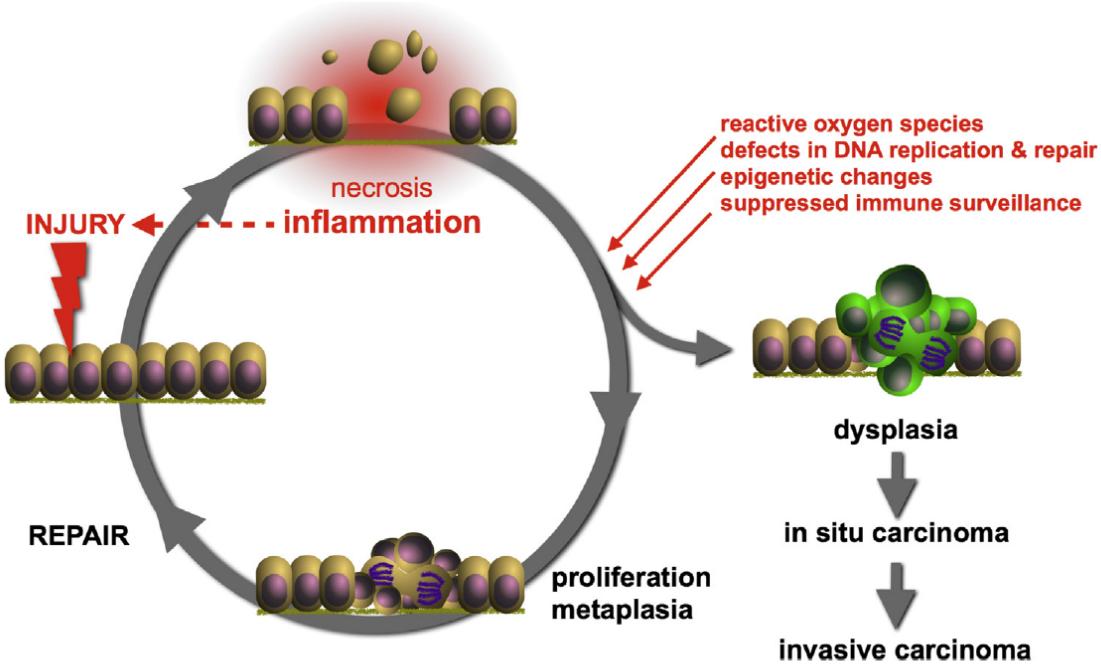

Fig. 1. Repetitive cycles of tissue **injury** and **repair** create a chronic inflammatory context with increased risk for malignant degeneration. Tissue injury can be initiated by environmental toxins, irradiation, carcinogens, and infection. The resulting **necrotic cell death** causes a release of pro-inflammatory mediators which aggravate tissue injury and recruit inflammatory cells such as tumor-associated macrophages and neutrophils. This is in sharp contrast to apoptotic cell death, which leads to a non-inflammatory removal of cellular material by phagocytes. Meanwhile, the loss of tissue integrity triggers a physiological **regenerative response** with activation of genes governing stem cell mobilization and proliferation. This is the critical phase in which potentially genotoxic inflammatory mediators (e.g. reactive oxygen species) can act and deviate the controlled proliferative response towards dysregulated cell proliferation and aberrant differentiation. Inflammatory mediators such as ROS and cyclo-oxygenase metabolites have the potential to induce changes at the epigenetic level, which will contribute to the instability of the normal injury-repair cycle. Finally, inflammatory leucocytes are functionally polarized towards angiogenesis, fibrosis and **suppression of adaptive immunity**. The suppressed anti-tumor immune surveillance is an additional factor allowing unchecked escape of the injury-repair process towards malignant progression.

Expériences de carcinogenèse physique avec certains corps étrangers chimiquement inertes

- Certains corps étrangers chimiquement inertes (cellulose, verre), implantés chez l'animal, peuvent induire des sarcomes
- Un même corps étranger, selon sa structure et sa taille (diamètre des pores, longueur des fibres) pourra induire ou non un cancer
- Une lignée cellulaire dérivée d'un polype adénomateux humain est non tumorigénique lorsqu'elle est implantée sous la peau chez des souris nude, alors qu'elle devient tumorigénique lorsqu'elle est implantée avec une plaque de plastique qui induit une forte inflammation

Un phénotype cancéreux peut être réversible si la cellule est replacée dans un environnement tissulaire normal

- Une lignée hépatique transformée donne des tumeurs agressives lorsqu'elle est implantée sous la peau de rats, alors qu'elle s'intègre dans le tissu hépatique et ne produit pas de tumeur lorsqu'elle est implantée dans le foie
- L'implantation sous la peau de cellules de tératocarcinomes (cellules embryonnaires malignes) donne des tumeurs contenant différents types cellulaires. Lorsque ces cellules sont implantées dans des blastocystes, elles participent au développement des souris parfaitement viables, mosaïques de cellules de tératocarcinomes et de cellules normales
- des cellules cancéreuses humaines, placées in vivo dans un environnement épithélial de glande mammaire de souris, peuvent se différencier en cellules épithéliales mammaires humaines qui s'incorporaient au tissu mammaire de souris et étaient capables de sécréter des protéines de lait humaines chez les souris

Nature des cibles de la cancérogenèse : sont-elles les cellules épithéliales ou le stroma (tissu conjonctif) de la glande mammaire ?

- Des combinaisons constituées de stromas exposés à un cancérogène, auxquels on ajoute des cellules épithéliales normales et non exposées, devenaient des néoplasmes
- La combinaison inverse (où des cellules épithéliales normales sont exposées à un cancérogène, alors que le stroma ne l'est pas) ne conduisait pas à la formation de néoplasme.
- Possibilité de « normaliser » le phénotype cancéreux en combinant des cellules de carcinome mammaire avec du stroma normal: les cellules tumorales généraient alors des canaux mammaires phénotypiquement normaux

The stroma as a crucial target in rat mammary gland carcinogenesis

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Summary

A complex network of interactions between the stroma, the extracellular matrix and the epithelium drives mammary gland development and function. Two main assumptions in chemical carcinogenesis of the mammary gland have been that carcinogens induce neoplasia by causing mutations in the DNA of the epithelial cells and that the alterations of tissue architecture observed in neoplasms are a consequence of this primary mutational event. Here, we use a rat mammary tissue recombination model and the chemical carcinogen *N*-nitrosomethylurea (NMU) to determine whether the primary target of the carcinogen is the epithelium, the stroma or both tissue compartments. Mammary epithelial cells were exposed in vitro either to the carcinogen or vehicle before being transplanted into the cleared fat pads of rats exposed to carcinogen or vehicle. We observed that neoplastic transformation of these mammary epithelial cells occurred only when the stroma was exposed in vivo to NMU, regardless of whether or not the epithelial cells were exposed to the carcinogen. Mammary epithelial cells exposed in vitro to the carcinogen formed phenotypically normal ducts when injected into a non-treated stroma. Mutation in the Ha-*ras*-1 gene did not correlate with initiation of neoplasia. Not only was it often found in both cleared mammary fat pads of vehicle-treated animals and intact mammary glands of untreated animals, but it was also absent in some tumors. Our results suggest that the stroma is a crucial target of the carcinogen and that mutation in the Ha-*ras*-1 gene is neither necessary nor sufficient for tumor initiation.

Key words: Mammary carcinogenesis, Stroma, Neoplasms, *N*-nitrosomethylurea, NMU, Ha-*ras*-1 mutation, Tissue architecture

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Cancer: the role of extracellular disease

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Summary Invasive carcinoma originates from the epithelial cells lining the lumen of an organ. It is often preceded by metaplasia, dysplasia or carcinoma in situ. The purpose of this review is to suggest that this disease of the epithelium may be, in part, the result of underlying tissue-based disorganization. Human cancer is frequently associated with pre-existing tissue disease. For example, hepatocellular carcinoma usually occurs in patients with a macronodular cirrhotic liver. Most lung cancers arise among patients with chronic lung disease (bronchitis, emphysema, and chronic infection). Mechanical forces appear to play a major role in regulating normal and cancer cell growth. The loss of cell polarity by neoplastic cells, coupled to an otherwise normal growth rate is enough to explain the cancer star-shaped pattern. By changing the plane of cell division, tumor cells may escape physical constraints from surrounding cells and divide. Loss of cell polarity and the resulting cell proliferation appears to be a consequence of either tissue-based disorganization (chronic inflammation, fibrosis) or of direct carcinogenic insult. The multiple mutations frequently described in cancer may be, in part, secondary to physical stress and not primary events. Several animal and clinical trials have shown that tissue disruption (i.e. radiation-induced fibrosis or liver cirrhosis) can be successfully treated. It is possible that treatment targeted at tissue disruption would delay or reduce cancer incidence regardless of the precise biological mechanism of carcinogenesis.

Tumor and Stem Cell Biology

Cancer Research

Reprogramming Human Cancer Cells in the Mouse Mammary Gland

Karen M. Bussard[1], Corinne A. Boulanger[1], Brian W. Booth[1,2], Robert D. Bruno[1], and Gilbert H. Smith[1]

Abstract

The tissue microenvironment directs stem/progenitor cell behavior. Cancer cells are also influenced by the microenvironment. It has been shown that, when placed into blastocysts, cancer cells respond to embryonic cues and differentiate according to the tissue type encountered during ontological development. Previously, we showed that the mouse mammary gland was capable of redirecting adult mouse testicular and neural stem/progenitor cells toward a mammary epithelial cell fate during gland regeneration. Here, we report that human embryonal carcinoma cells proliferate and produce differentiated mammary epithelial cell progeny when mixed with mouse mammary epithelial cells and inoculated into the epithelium-free mammary fat pads of athymic nude mice. Fluorescence *in situ* hybridization confirmed the presence of human cell progeny in the mammary outgrowths for human centromeric DNA, as well as immunochemistry for human-specific breast epithelial cytokeratins and human-specific milk proteins in impregnated transplant hosts. It was found that the number of human cells increased by 66- to 660-fold during mammary epithelial growth and expansion as determined by human cytokeratin expression. All features found in primary outgrowths were recapitulated in the secondary outgrowths from chimeric implants. These results show that human embryonal carcinoma–derived progeny interact with mouse mammary cells during mammary gland regeneration and are directed to differentiate into cells that exhibit diverse mammary epithelial cell phenotypes. This is the first demonstration that human cells are capable of recognizing the signals generated by the mouse mammary gland microenvironment present during gland regeneration *in vivo*. *Cancer Res; 70(15); 6336–43. ©2010 AACR.*

Place des anomalies génétiques

- **L'état prolifératif serait l'état basal, par défaut, de toute cellule.**
- L'organisation des cellules en tissu constituerait un frein à la prolifération, et les agents induisant une perturbation de l'organisation tissulaire, en levant ce frein, entraîneraient une reprise de prolifération.
- Les mutations ne seraient alors qu'une conséquence de cette prolifération exacerbée, qui pourrait favoriser les erreurs lors de la réplication de l'ADN.

Tentatives de réconciliation

- prise en compte du microenvironnement cellulaire par les tenants de la théorie des mutations somatiques
- rôle de la production des radicaux libres liés aux processus inflammatoires dans l'apparition des mutations
- prise en compte grandissante des phénomènes épigénétiques

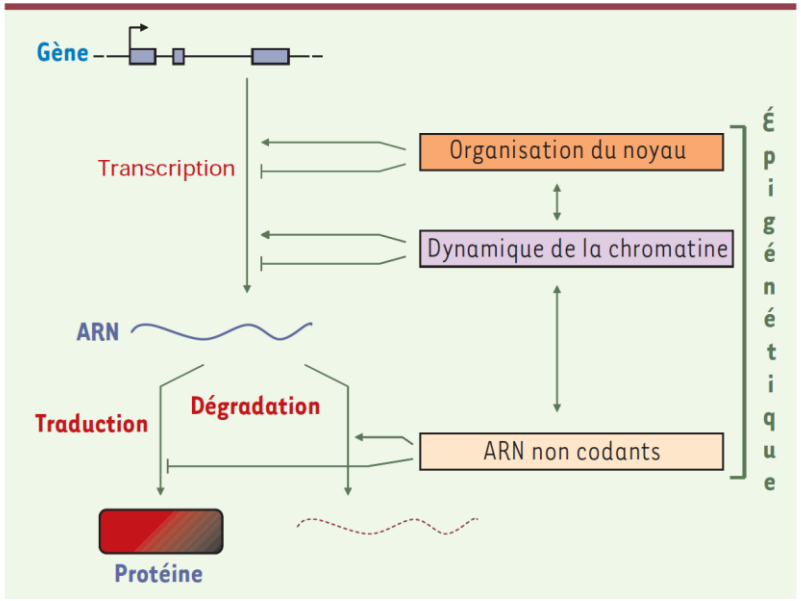
Modifications épigénétiques et variabilité phénotypique

- Modifications épigénétiques de la chromatine
- Le paysage épigénétique, ou épigénome, est stable et reproductible dans les cellules différenciées normales, mais aberrant dans les cancers
- Interconnexion de ces deux types d'événements aléatoires dans le cancer

Les phénomènes épigénétiques

Rôle dans la diversification fonctionnelle de cellules cancéreuses qui ont acquis des phénotypes très différents malgré un génome stable

- Méthylation de promoteur de gène par la DNA-méthyltransférase
- Histones
- ARNs non-codants (silencieux): miR
- Longs ARNs non-codants



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Le double jeu de l'épigénétique

Cible et acteur du cancer

Sophie Laget, Pierre-Antoine Defossez

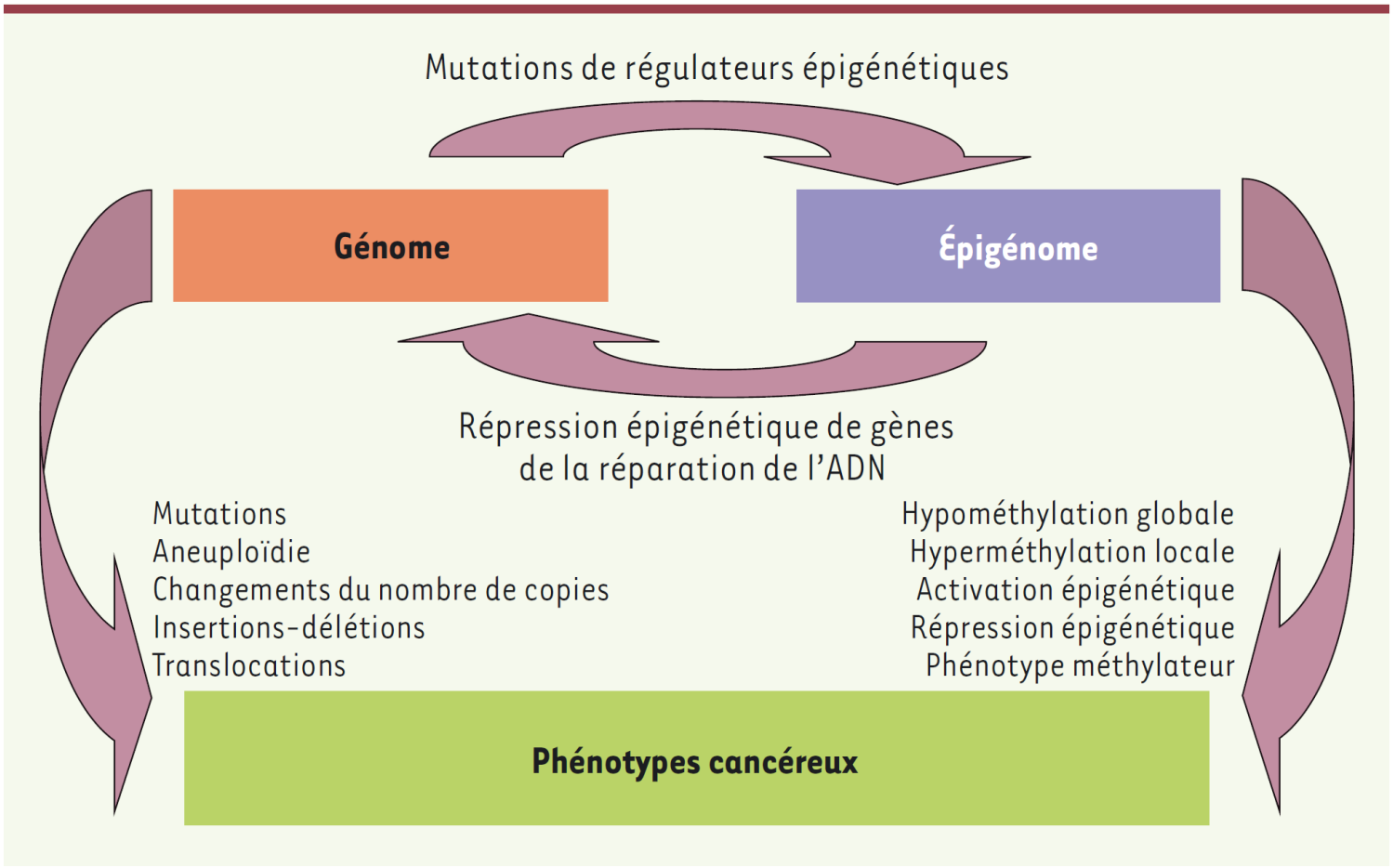


Figure 1. ***Les événements génétiques et épigénétiques aléatoires contribuent à l'apparition des phénotypes cancéreux.*** De plus, ils s'influencent réciproquement au travers de modifications génétiques de gènes codant pour des modificateurs de la chromatine, ou de modifications épigénétiques de promoteurs de gènes de la stabilité génétique (adapté de Shen et Laird [12]).

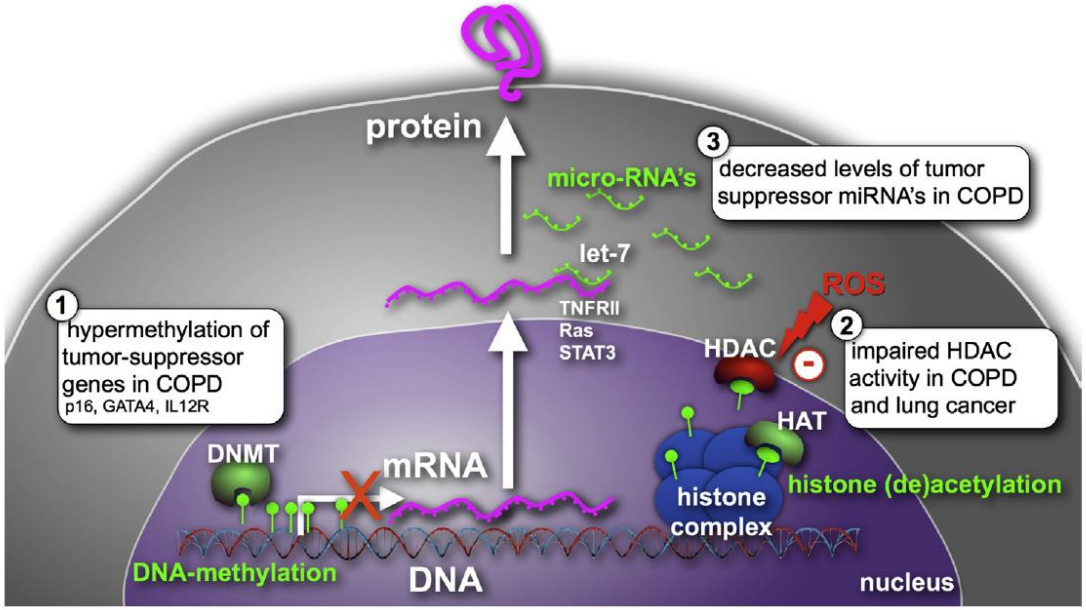


Fig. 5. Several epigenetic events are shared by COPD and lung cancer. (1) **DNA-methyltransferases** (DNMTs) modify the methylation status of CpG-rich regions in gene promotors. Promotor hypermethylation of tumor-suppressor genes is an event that is already observed in COPD airways. (2) Modulation of histone protein acetylation is controlled by **histone acetylases** (HATs) and **deacetylases** (HDACs), results in "opening" respectively "closing" of the chromatin, hence modulating access of transcription factors to their promotor or enhancer regions. The role of HDACs in regulating inflammation and oncogenesis is complex (see main text). One scenario involves reactive oxygen species, generated as a by-product of chronic inflammation, which are able to sabotage the function of HDACs, resulting in impaired transcription of tumor-suppressor genes in COPD and lung cancer. (3) Translation of messenger mRNA into protein is regulated by **micro-RNAs**, which bind consensus sequences on the 3′-end of specific mRNAs, leading to a translation stop or degradation of the mRNA:miRNA complex. **Let-7** is an miRNA species, which represses translation of genes involved in inflammation and cancer. Let-7 has been validated as a tumor-suppressor miRNA in lung cancer, and its levels are reduced with increasing COPD severity.

Approche post-réductionniste

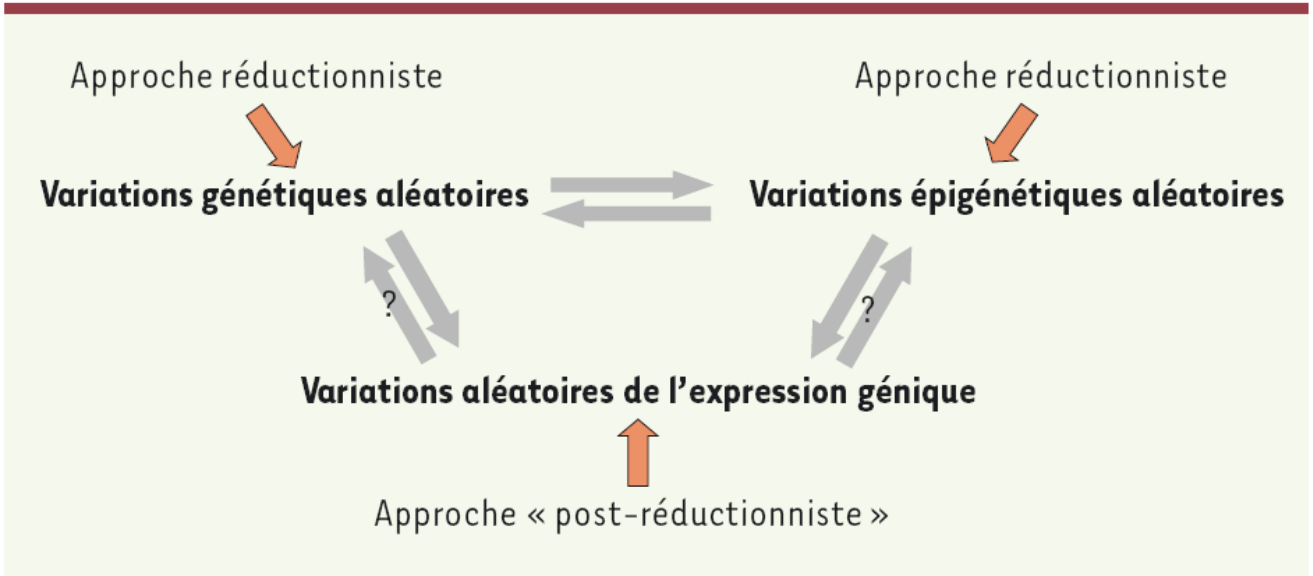


Figure 2. ***Les trois types d'événements aléatoires étudiés ici sont interconnectés.*** Seul l'impact des variations aléatoires de l'expression génique sur les variations génétiques et épigénétiques restent à démontrer. Dans le cas du cancer, les différentes entrées dans ce cercle correspondent à des approches différentes. Alors que les théories génétiques et épigénétiques du cancer relèvent d'un schéma réductionniste, donner aux variations aléatoires de l'expression génique un rôle causal permet de dépasser les schémas réductionnistes. En effet, de fortes variations d'expression pourraient trouver leur origine dans le fait que les cellules ne seraient pas ou plus en mesure de stabiliser leur expression génique par la mise en place d'interactions cellulaires (si celles-ci sont perturbées par des agents chimiques par exemple). Ainsi l'interconnexion des niveaux génique et tissulaire est considérée comme primordiale et aucun niveau d'organisation n'est privilégié.

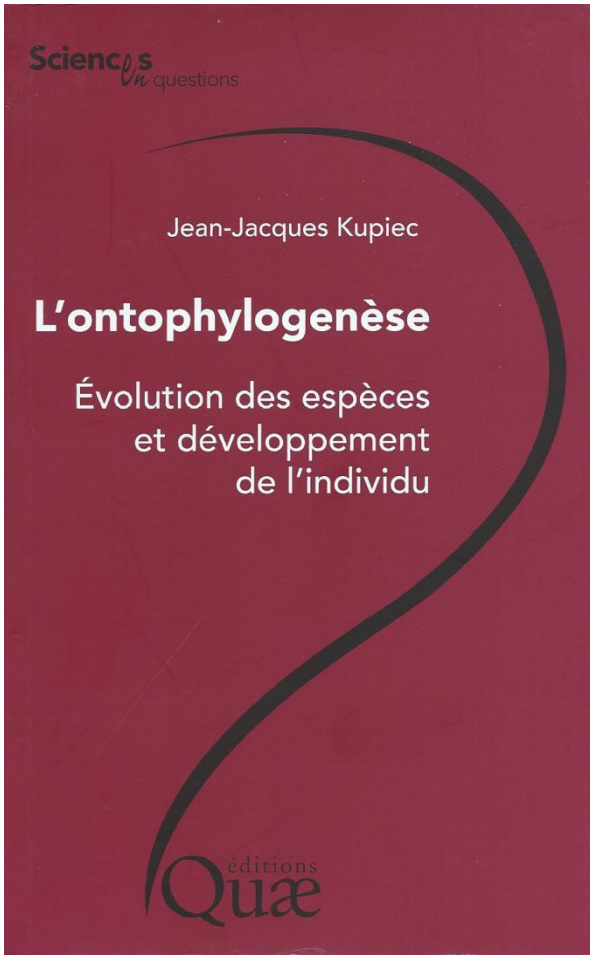
variations **aléatoires** de l'expression génique entre cellules

- La pluripotence des cellules souches serait le fruit d'un état d'instabilité intrinsèque de l'expression des gènes, responsable lui-même du grand nombre de voies développementales possibles pour ces cellules.
- Cette instabilité serait donc une propriété statistique des populations de cellules souches, mais ne pourrait pas être définie au niveau individuel du fait de la variabilité intrinsèque de ces cellules

La différenciation cellulaire représenterait le passage d'un état permissif de la chromatine permettant cette expression généralisée et variable vers un état contraint (fermé), qui limite la variabilité d'expression dans le cadre d'une régulation spatiotemporelle de cette variabilité au cours du développement

Théorie de l'ontophylogenèse

- Au niveau moléculaire et tissulaire
- La stochasticité de l'expression des gènes au sein des cellules indifférenciés permet un processus sélectif au niveau cellulaire aboutissant à la stabilisation de l'expression d'un panel de gènes adaptés à un environnement donné grâce aux interactions établies par la cellule avec cet environnement



Rôle de la signalisation cellulaire issue des interactions cellulaires dans la phase de stabilisation de l'expression génique au cours du développement

ARTICLES

nature
cell biology

Cell-to-cell expression variability followed by signal reinforcement progressively segregates early mouse lineages

Yusuke Ohnishi[1], Wolfgang Huber[2], Akiko Tsumura[3], Minjung Kang[4], Panagiotis Xenopoulos[4], Kazuki Kurimoto[5,6], Andrzej K. Oleś[2], Marcos J. Araúzo-Bravo[7], Mitinori Saitou[3,5,6,8], Anna-Katerina Hadjantonakis[4] and Takashi Hiiragi[1,9]

- l'état cancéreux correspond à un retour à un état permissif de la chromatine et à *une perte de l'information développementale*

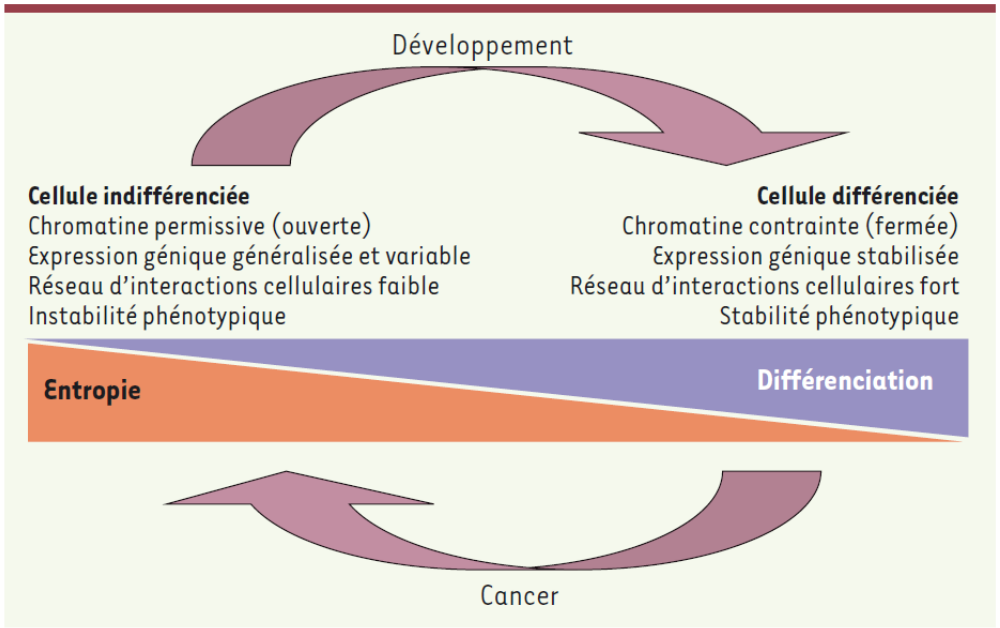


Figure 3. ***Les cellules indifférenciées présentent des caractères phénotypiques instables en raison de l'expression généralisée et variable de leur génome.*** Celle-ci est due à une chromatine permissive, elle-même liée au faible réseau d'interactions cellulaires autour de ces cellules qui ne permet pas les signalisations nécessaires à la stabilisation de l'expression. Au cours du développement et de la différenciation, la mise en place d'interactions cellulaires stabilise l'expression des gènes et ainsi les phénotypes cellulaires. La chromatine devient plus contrainte et fermée. Si les interactions cellulaires sont perturbées, les cellules redeviennent instables aux niveaux de l'expression génique et phénotypique, ce qui correspond à une dédifférenciation. Ces cellules risquent alors de se transformer en cellules cancéreuses si elles contiennent déjà, ou en acquérant, des altérations génétiques et/ou épigénétiques. Ce phénomène est aussi possible si des cellules souches restent indifférenciées parce qu'elles ne peuvent pas établir les interactions cellulaires nécessaires à leur différenciation (adapté de MacArthur et Lemischka [25] et de Capp [28]).

- Le cancer peut donc être considéré comme une maladie du développement et de la différenciation
- Toute molécule capable d'altérer les membranes cellulaires, jonctions cellulaires, molécules d'adhésion, ou encore les molécules solubles comme les hormones ou les facteurs de croissance (qui diffusent entre les cellules et constituent un mode d'interactions à distance), pourrait être capable d'enclencher un processus de cancérogenèse

- La variabilité génétique et épigénétique des cellules cancéreuses pourrait d'ailleurs trouver son origine dans l'expression plus variable des gènes impliqués dans les voies qui maintiennent la stabilité du génome ou de l'épigénome
- l'apparition aléatoire de mutations ponctuelles ou d'altérations chromosomiques pourrait se produire en réponse aux perturbations des voies de maintien de l'intégrité du génome que provoquerait l'expression fortement aléatoire des gènes impliqués dans ces voies.
- Il s'agirait surtout d'un phénomène inéluctable lorsque l'expression génique est fortement instable. La sélection d'altérations génétiques et épigénétiques aurait ensuite lieu en fonction de la pression sélective

Réconciliation

- entre l'organisme et les gènes : la cellule
- Rôle de l'environnement interne, aussi bien dans la croissance des tumeurs que dans le développement des métastases. La notion de niche est de plus en plus utilisée pour désigner ce microenvironnement favorable à la croissance de la tumeur ou à la formation de métastases, comme elle l'est, et non sans lien, dans le cas des cellules souches.
- Le rôle de cet environnement peut être vu de manière classique, comme intervenant dans le tri des mutations se produisant dans les cellules cancéreuses. Il peut être imaginé de manière moins traditionnelle, comme modifiant le taux de mutations des cellules tumorales ; ou comme créant des épimutations (par modifications épigénétiques) dont les effets peuvent être similaires à ceux des mutations.

Leading Edge
Essay

Cell

Coming Full Circle—From Endless Complexity to Simplicity and Back Again

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Cell has celebrated the powers of reductionist molecular biology and its major successes for four decades. Those who have participated in cancer research during this period have witnessed wild fluctuations from times where endless inexplicable phenomenology reigned supreme to periods of reductionist triumphalism and, in recent years, to a move back to confronting the endless complexity of this disease.

Search Results

Cancer research pioneer Robert Weinberg corrected Oncogene paper

with 3 comments

Robert Weinberg, a prominent cancer researcher at the Whitehead Institute, issued a correction to a paper in *Oncogene* in May, fixing two errors missed during proofing.

We found this one a little late, obviously. It also appears to be a relatively minor correction, not one that appears worthy of retraction. We've gotten feedback from readers asking why we cover corrections; we chose to flag this one because Weinberg has had such an impact on his field — he discovered the first tumor–causing gene in humans, as well as the first tumor–suppressor gene — and his papers are often highly cited. He also has issued five retractions in the past, most of which for papers whose first author was a member of his lab, who is not a co–author on the *Oncogene* paper.

Here's the correction note for "Thrombospondin–1 repression is mediated via distinct mechanisms in fibroblasts and epithelial cells:"

Read the rest of this entry »

Written by Shannon Palus
December 14th, 2015 at 11:30 am

Posted in cancer biology,corrections,freely available,nature publishing group,oncogene (journal),robert weinberg,united states

Cancer Research retraction is fifth for Robert Weinberg; fourth for his former student

with 4 comments

Another domino has fallen in a chain of retractions for Robert Weinberg, the man who discovered the first tumor-causing gene in humans, along with the first tumor suppressor gene: *Cancer Research* just retracted a paper of his on some of the molecular steps to metastasis.

The paper, "Concurrent Suppression of Integrin α_5, Radixin, and RhoA Phenocopies the Effects of miR-31 on Metastasis," has been cited 70 times, according to Thomson Scientific's Web of Knowledge. As we have noted before, Weinberg's papers are frequently highly cited. His bio at the Whitehead Institute bills him as "a pioneer in cancer research."

Four of Weinberg's retracted papers — including this latest — share a first author: Scott Valastyan, once a very promising grad student in Weinberg's lab.

This retraction, like Valastyan's others, is linked to his retracted 2009 *Cell* paper. (That paper was cited 482 times, and there's even a video from the *Cell* press office to go with it). Read the rest of this entry »

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Written by Shannon Palus
July 6th, 2015 at 11:30 am

Posted in cancer biology,cancer research,freely available,methodological problems,molecular biology,robert weinberg,society journal retractions,united states

Other shoe drops for MIT cancer researcher Robert Weinberg as Cell retraction appears

with 21 comments

Robert Weinberg, a prominent cancer scientist whose papers often notch hundreds or thousands of citations, has lost a fourth paper, this time a 2009 publication in *Cell*.

Journal *Genes and Development* pulled two of Weinberg's papers in March, stating that they had retracted the 2009 study because data from several experiments was used in figures that seemed to represent only one. The *Genes and Development* papers were sunk because the "same analytical methodology was used."

At the time, the *Cell* retraction was unavailable, though a spokesperson informed us it was forthcoming. The paper has been cited 482 times, according to Thomson Scientific's Web of Knowledge.

Now that the notice has landed, here's why the paper is being retracted: Read the rest of this entry »

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Written by Cat Ferguson
April 3rd, 2015 at 11:35 am

Posted in cell,cell biology,elsevier,freely available,image manipulation,robert weinberg,united states

Two more retractions appear for prominent MIT cancer researcher Robert Weinberg

with 8 comments

Two identical retraction notices have popped up for MIT professor Robert Weinberg, a highly-cited cancer researcher who had a retraction and a correction in 2013, both in *Cancer Cell*.

These two new retractions, in *Genes and Development*, stem directly from another paper by Weinberg and colleagues in *Cell* that will apparently be retracted, as the "same analytical methodology was used," according to the notices [see bottom of the post for an update].

Weinberg is highly regarded, and at least 20 of his papers have been cited over a thousand times.

First author Scott Valastyan was a promising postdoc at the time of the paper's publication. He was a 2011 Runyon Fellow at Harvard, a three-year, $156,000 award for outstanding cancer postdocs. He doesn't seem to have published anything since 2012, though he is listed as a joint inventor with Weinberg on patents filed in 2009 and 2014.

Here are the notices for "Concomitant suppression of three target genes can explain the impact of a microRNA on metastasis" (cited 73 times, according to Thomson Scientific's Web of Knowledge) and "Activation of miR-31 function in already-established metastases elicits metastatic regression" (cited 54 times), both paywalled:
Read the rest of this entry »

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Written by Cat Ferguson
March 19th, 2015 at 12:45 pm

Posted in behind a paywall, genes & development retractions, image manipulation, oncology retractions, oxford university press, robert weinberg, united states