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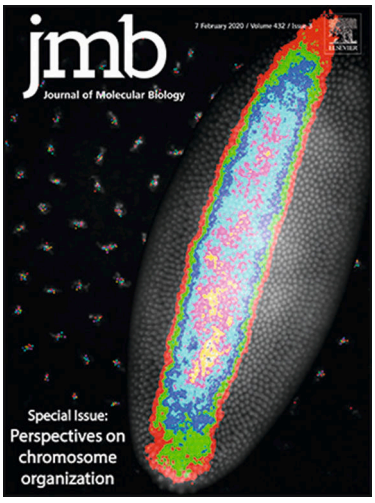

Review Article

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Epigenetic "*Drivers*" of Cancer

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Abstract
Genetics is at the basis of cancer initiation and evolution, but emerging evidence indicate that mutations are not sufficient to produce cancer, indicating a role for epigenetic contributions to the different stages of tumorigenesis. While the genetic tracks of cancer have been widely investigated, the epigenetic "drivers" remain a vague definition. Gene-environment interactions can produce gene-regulatory programs that dictate pathogenesis; this implies a reciprocal relationship where environmental factors contribute to genetic mechanisms of tumorigenesis (i.e. mutagenesis) and genetic factors influence the cellular response to extrinsic stress. In this review article, we attempt to summarise the most remarkable findings demonstrating a contribution of epigenetic factors as proper "drivers" of tumorigenesis. We also try to pose attention on the relevance of epigenetic mechanisms as downstream consequences of genes versus environment interaction.

Cancer: an *(epi)genetic disease*?

Despite cancer has been for long acknowledged as a disease with genetic basis and large efforts have been invested in defining its genetic tracts[1][2], alterations of the cellular epigenome have emerged as potential "driver" factors in its pathogenesis [3]. Integration of extrinsic and intrinsic factors equally contribute with a reciprocal relationship: somatic mutations can alter integration of external stressors, while stressors can concur to promote genetic evolution (i.e. new mutations). A recent study is among the first to formally demonstrate that gene–environment interactions can rapidly produce gene-regulatory programs that dictate early neoplastic commitment [4]. Extrinsic factors (injury) trigger a rewiring of the chromatin landscape only if specific genetic pre-malignant mutations (KRas) are present in genetic background, thus triggering tumorigenesis as a proper "driver" event. Interaction between genes and environment has far reaching consequences; behavior of cancer mutations can also be influenced by environmental factors; for example somatic mutations in p53 have shown plasticity (switch from oncosuppressive to oncogenic) in different microbiome contexts [5,6], while the same mutations have also shown ability to deregulate response to microenvironmental stressors, such as hypoxia [7–12]. Mutations directly affecting epigenetic enzymes or histones have been postulated in the last decades to contribute to the evolution and heterogeneity of cancer (**Figure 1 and Box 1**); hence in the most classical view direct epigenetic alterations playing a role in tumorigenesis can derive from mutational events on genes codifying for epigenetic regulators. Thus, a genetic-epigenetic circuit underlies the molecular basis of cancer at different stages. These clear evidence of an epigenetic contribution to initiation and progression of cancer and the determination of a synergistic effect of sporadic mutations and extrinsic stressors provide rationale for investing efforts in these directions to design of early detection and treatment strategies.

In this review, we focus the epigenetics of cancer by discussing how interactions between environment and genes can impinge on the epigenetic code and trigger disease. We also report a selection of the most frequently observed mutations of epigenetic factors, that appear as causative direct events in the pathogenesis. We finally describe the advances of the strategies for the study of the cancer-associated chromatin landscape and discussing the strict correlation between epigenetics, DNA damage and genomic integrity.

Epigenetic rewiring in cancer: consequence of mutations or response to stressors?

The assay for transposase-accessible chromatin followed by sequencing (ATAC-seq) is among the current best methods to assess genome-wide chromatin accessibility. Many regions of cancer genomes, particularly in non-coding areas, acquire accessibility if compared to the normal tissue counterpart. Integration of ATAC-seq with GWAS analysis identified non-coding mutations in regulatory regions associated with a significant gain of chromatin accessibility which results in changes in the expression of nearby genes. On the basis of different chromatin accessibility landscapes, it has been also possible to define new tumor subtypes, for breast cancer, prostate adenocarcinoma and kidney renal papillary cell carcinoma [13]. Hence, epigenetic rewiring appears a hallmark of cancer, of high importance for understanding the molecular basis of prognosis and response to therapies [13,14].

In a recent PAN-Cancer study, Chen and colleagues have reported a substantial variation of enhancer elements, resulting in the alteration the profile expression of the associated genes. Several enhancers in each cancer type strongly and negatively correlated with patient survival [15]. Therefore, DNA enhancer elements potentially represent a reliable signature of cancer prognosis. Single nucleotide polymorphisms (SNPs) are also frequently observed in accessible enhancers, regulating the open/close status of these regulatory elements. Some of these SNPs have been associated with risk to develop specific types of cancer (for instance rs6983267 for breast cancer, rs35252396 for kidney renal clear cell carcinoma, rs4444235 for colorectal cancer) [15,16].

During the last decade, genome-wide analyses have identified driver mutations in genes regulating the epigenetic processes, which can induce particular chromatin landscapes that may support tumorigenesis [17]. Remarkably mutations have also been reported in genes codifying for histones. Somatic mutations observed in paediatric brain tumours in the *H3F3A* gene, coding for the histone variant H3.3, are a prototype example of histone mutations. These involve the aminoacidic substitution K27M (lysine to methionine at position 27) and G34R/V (glycine to arginine/valine at position 34). Notably, the two mutations have been found in tumors affecting different areas of the brain: K27M mutation occurs in tumors of spinal cord, thalamus, pons and brainstem; while G34R/V expressing tumors are located in the hemispheres [18,19]. Mutated H3.3 histone, also defined oncohistone, promotes tumorigenesis affecting multiple mechanisms, linked to global loss of H3K27me3 mark, which is caused by the direct inhibition of $H3.3^{K27M}$ on EZH2, a component of the Polycomb Repressive Complex 2 (PRC2). Also, focal H3K27me3 acquisition is observed in the promoters of tumor suppressor genes such as the *INK4A/ARF* locus [20]. The $H3.3^{G34R/V}$ oncohistone has been associated with loss of H3K36me3 mark due to the abrogation of the methyltransferase activity of SETD2. Yang and colleagues reported that the oncohistone physically blocks the K36 pocket domain, therefore inhibiting the aminoacidic residue methylation [21].

Mutations in the linker histone H1 isoforms B-E (H1B, H1C, H1D and H1E; also known as H1-5, H1-2, H1-3 and H1-4, respectively) are highly recurrent (30-40%) in B cell lymphomas [22]. Disruption of H1 function produces substantial alterations in the chromatin architecture, leading to large-scale shifts of chromatin from a compacted to a relaxed state. These changes result in gain of H3K36me2 and/or loss of repressive H3K27me3, unlocking expression of stem cell genes that physiologically undergo silencing during early development. This enhanced fitness and self-renewal properties, ultimately produce aggressive lymphomas with an increased repopulating potential in mice models of H1c and H1e deficiency [23][24].

Point mutations can also occur in canonical histones. The overall mutation rate of histone genes ranges from 8% in the cervix tumor to less than 1% in myeloid cancers [25]. In the very last years, H2 histone has attracted much interest. In particular, the missense mutation glutamate-to-lysine at position 76 of histone H2B ($H2B^{E76K}$) has been observed in a variety of cancers. The particular feature of $H2B^{E76K}$ is to impair the histone octamer and nucleosome assembly which inhibits DNA compaction, consequently, resulting into an increased chromatin accessibility and gene expression [25]. Short H2A (sH2A) variants are a subclass of histone that display oncohistone features such as missense substitutions. Their role in tumorigenesis is not fully understood, but it is reported that they are linked to aberrant splicing given their capacity to bind RNA and splicing factors [26]. How integrations of extrinsic stressors occur on mutant histones containing chromatin is yet to be understood.

Alonso-Curbelo and colleagues have very recently provided one of the first formal proof that interaction of extrinsic factors (injury) and genetic mutations (KRas mutation) can trigger a rewiring of the chromatin landscape, that acts a driver event of the tumorigenesis. In an *in vivo* pancreatic cancer model, under perturbed conditions, such as mutation of *KRAS* and simultaneous tissue damage, the chromatin undergoes a complete remodeling, producing a cancer-specific transcriptional program. The results of this study have the important implications of demonstrating that altered genetic background (pre-malignant KRas mutations) influences integration in the cellular epigenome of the response to extrinsic factors (injury). At the same time these results support the postulation that epigenetic mechanisms can represent early stage drivers of the tumorigenesis [4][27–29]. A wide range of (micro)-environmental factors can influence the cellular epigenome with different implications for cancer and normal cells. A remarkable and not yet deeply dissected contribution might derive from commensal microbiome [30–32], which influences tumorigenesis with a not clearly dissected mechanisms. At the same time integration of detoxification systems [33,34]

and dietary components might indirectly influence the response to injury, through the regulation of cellular epigenome with mechanisms never conceived.

Metabolic stress, nutrient status and oxygen sensing: is epigenetic the causative link to cancer?

DNA and histone post-translational modifications require metabolic substrates. S-adenosyl methionine is the main methyl-donor for methylation of DNA (cytosine) and histones; acetyl-CoA is required for acetylation and alfa-ketoglutarate for de-methylation reactions. Metabolic deregulations, associated to cellular metabolic status or functional alterations of the metabolic enzymes, influence the epigenetic pattern of the cells. General stress conditions can also influence directly or indirectly the epigenetic modifications. For example, TET-mediated de-methylation of 5-methyl-cytosine requires oxygen and α-ketoglutarate (α-KG) from the tricyclic acid cycle (TCA) as substrates, generating CO_2 and succinate as products. Hence, oxidative stress or reduced oxygen tension (hypoxia) can generate unbalance in the activity of DNMTs and TET resulting in a global perturbation of the epigenetic landscape [35] [36–39]. The JmjC-containing enzymes, lysine demethylase 5A (KDM5A) can sense oxygen deprivation and reprogram chromatin state. Hypoxia induces a rapid induction of histone methylation on H3K4 and H3K27, which is mediated by the inactivation of KDM5A [40]. Similarly, KDM6A seems to sense oxygen concentration and influence the methylation pattern of histones [41].

A number of compelling examples indicate correlative observations between metabolic status, oxygen supply and epigenetic regulations, while causative relationships, with directional links remain to be determined. Moreover, causality of these events, and therefore a link to lifestyle and diet, to cancer susceptibility, is yet elusive.

Genome integrity: epigenetic regulators of DNA damage response

The genome is constantly exposed to endogenous and exogenous harmful stressors [42]. Mechanisms involved in the DNA damage response (DDR) evolved to ensure maintenance of genome stability. During the last two decades, studies have described a tight coordination between genome and epigenome in the preservation of cell function and identity [43]. Several histone modifications, histone modifying and chromatin remodeling enzymes normally involved in the control of gene expression, play a fundamental role in the DNA repair processes [43,44]. A variety of post-translational modifications such as phosphorylation, ubiquitylation, acetylation, ADP-ribosylation have been extensively described to regulate and facilitate the DNA repair process [44]. Of note many factors including histone deacetylases and methyltransferases control spatiotemporally the reactions necessary for accurate repair of the DNA damage. For instance, Polycomb Group proteins (PcG), commonly involved in the gene silencing, have been found to damage foci. In particular, the ubiquitylation of H2A by Polycomb repressor complex 1 (PRC1) exerts a dual role: it is a mark for transcriptionally inactive chromatin and acts as a mark of DNA damage [45]. Also the histone methyltransferases SETDB1 and SUV39 contribute to DDR, with a proposed model by which transiently compact the chromatin to promote homologous recombination (HR). SETDB1 and SUV39 are indeed dispensable for non-homologous end joining (NHEJ) but appear essential for HR [46].

A plethora of in vitro and *in vivo* studies have demonstrated the role of SWI/SNF complex to maintain genomic integrity by, in part, regulating the DNA damage response (DDR). More in detail, subunits of the BAF complex (SWI/SNF family) have been described to control the efficiency of non-homologous end joining (NHEJ) and homologous recombination (HR). For instance, ARID1A is responsible for the chromatin relaxation nearby the site of damage, a process required for the access of the NHEJ mediators, such as 53BP1 and RIF1 [47].The dysfunction of SWI/SNF complexes, as well as INO80, ISWI and CHD, can result in high rates of genetic mutations which may drive the cancer onset and development [48].

Genome integrity: epigenetic maintenance of heterochromatin

Link between epigenetic mechanisms and genomic integrity also exists in the regulation of genomic repetitive sequences, which are largely represented by interspersed LTR-based endogenous retroviruses (ERVs; 8% of genome) and non-LTR-based short- and long-interspersed nuclear elements (SINEs and LINEs, respectively; 35% of genome). Repetitive elements play major role in genome evolution and diversity, but their epigenetic regulation is of pivotal importance for maintenance of genomic stability and chromosome architecture. Repetitive elements expose genome to replication fork stalling and non-allelic recombination events, thus posing a major threat to genome integrity [49]. FBOX44 has been very recently associated to the regulation of repetitive elements. FBOX44 transcriptionally silences repetitive elements, binding histone trimethylated lysine 9 of the histone H3 at the replication fork. This triggers recruitment of SUV39H1, CRL4, and Mi-2/NuRD to transcriptionally silence REs post-DNA replication (**Figure 2**) [50].

Emerging role of specific DNA:RNA structures, called R-loops, are described in the regulation of physiological and pathological conditions [51]. In particular, R-Loops are three-stranded nucleic acid structures composed by a very stable pairing of RNA with a single DNA strand, displacing at the same time the other DNA strand (ssDNA) [52]. They can be present in the human genome also in physiological conditions; indeed the 5% of genome regions present these particular structures [53,54]. R-loops have been described to regulate many cellular processes such as replication, transcription and termination [55]. Particularly, Ginno et al. have demonstrated that R-loops found at gene promoters, enhance the transcription by protecting regions of DNA characterized by asymmetry of cytosine guanosines (CG skew) from methylation and therefore from silencing [56]. Moreover, R-loops decrease the promoter methylation resulting in an increased expression of a variety of genes [57]. R-loops can also direct the regulation of chromatin architecture and cellular differentiation. In particular Chen et al. have described the high importance of R-loops in coordinating these processes in embryonic stem cells. Indeed the authors have observed an enrichment of the occupancy of the complex Tip600-p400 and lower binding of PRC2 at genes whose proximal promoter is occupied by R-loops [58]. Beyond their physiological role, R-loops represent a continuous threat for genomic integrity. Epigenetic perturbations affecting transcription of codifying and non-codifying sequences (lnRNAs and repetitive elements) can lead to accumulations of unscheduled pathological R-loops. At least two are the mechanisms proposed for the R-loop mediated genomic instability: firstly, the displaced single strand DNA (ssDNA) is more susceptible to damage and can be abnormally recognized by mutagenic cellular enzymes such as cytidine deaminases; secondly, R-loops can cause replication stress inducing breaks and triggering unproper repair [59]. The role of R-loops in causing DNA damage has been extensively addressed. Recent studies from prokaryotic and eukaryotic mammal cells have highlighted that DNA damage and deregulation of repetitive sequences can lead to formation of R-loops [60–62]. Given their role of continuous source for genome integrity, R-loops removal is strictly controlled. Notably, few studies have evidenced the involvement DNA repair proteins in the suppression of R-loops. For instance, the factors BRCA1 and BRCA2, FANCD1, FANCD2 and FANCA, involved in the homologous recombination repair and in the Fanconi Anemia pathway, strongly suppress R-loop formation. Indeed, when one of these proteins is missing cells aberrantly accumulate R-loops and undergo DNA damage, as assessed by an increase of γH2Ax [63–65].

Polycomb proteins: key regulators of epigenetic states.

The cellular epigenome is maintained by a fine balance of extrinsic factors and their integration cells mediated by epigenetic modifiers and cellular signaling [66] and the Polycomb group proteins (PcG) play a key role in this process by ensuring correct development and differentiation epigenetic status [67,68]. PcG proteins are assembled in two large multimeric complexes, named PRC1 and PRC2, and are responsible for deposition of H3K27me3 and H2AK119Ub marks via EZH2

and RING1A/1B respectively. These are frequently deregulated or mutated in tissue with high renewal capacity such as hematopoietic compartment. PRC alterations are indeed very common in hematological tumors [69]. *In vivo* studies have helped in dissecting the role of PRC complexes: specific knocking out/overexpressing of different subunits/cofactors of PRC1 in mouse models demonstrated its oncogenic potential on the cell transformation. *In vivo* enforced expression of Cbx7 results in the development of a highly aggressive B cell lymphomas [70]. In particular, Cbx7 cooperates with c-Myc in accelerating lymphomagenesis. Cbx7 expressing tumors are characterized by high proliferation index and low apoptosis rate [70]. Moreover, loss of Ring1b, associated with deficiency of Ink4a, causes an acceleration of hematopoietic neoplasias. The data unveil the essential role of Ring1b in the negative regulation of myeloid cell proliferation. Interestingly, cells derived from Ring1b-deficient mice present a significant upregulation of Cyclin A and D, explaining the enhanced proliferation after Ring1b loss [71].

Bmi-1 has been the first component belonging to PRC1 to be identified in mammals [72]. Early *in vivo* studies have evidenced the oncogenic role of Bmi-1 in a mouse model of lymphomagenesis. Particularly, Bmi-1 was shown to inhibit the c-Myc induced apoptosis [73,74]. A later study has linked Bmi-1 overexpression to intestinal cancer. Loss of Bmi-1 significantly reduces the number of intestinal adenomas through an increased susceptibility to undergo apoptosis. This is a result of an increased expression of $p16^{INK4A}$/$p19^{ARF}$ locus which in turn stabilizes p53 protein to exert the apoptotic program [75].

Genetic studies of PRC2 components have documented loss of differentiation capacities, associated with increased cell proliferation and transformation. Different groups have demonstrated that both overexpression and loss of EZH2 lead to acute T-cell lymphoma (T-ALL), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms [76–78]. Furthermore, Berg et al. have provided functional insight in the Y641F activating mutation of EZH2 subunit. Mutation alone is not able to initiate lymphomagenesis, but concurrently to Myc overexpression, the tumorigenic process is dramatically enhanced [79]. PRC2 alterations have been also observed in solid tumors. In particular in breast cancer, EZH2 targeted overexpression in the mouse mammary gland disrupts the epithelial morphology. Moreover, EZH2 causes an accumulation of beta-catenin, by a direct interaction. The enhancement of the Wnt/β-catenin signaling leads to hyperplasia, the earliest recognizable marker of breast carcinoma [80].

Conclusions

Cancer epigenetics has represented an expanding field for the last decades, however this has not clearly impacted practical applications in patients' management. In the current post genomic cancer era, the following layer of information to comprehensively map cancer is a detailed dissection and integration of the epigenome. The significant development of genomic techniques which has been seen in the last years is providing the scientific community with the right tools to this goal. Ultimately, this information will have to be translated into patients benefit. While however the last decades have seen a great emphasis on the development of "epigenetic therapies", the future should significantly look into the potential of epigenetic marks as early-stage biomarkers of disease or of therapeutic response.

BOX 1: DNA methylation

The presence of a methyl group on the position 5' of the cytidine (5-mC) represents a major repressive epigenetic mechanism involving DNA modification, in particular in the cytidines and guanidines rich sequences (CpG islands) [81,82]. This regulation is tightly controlled by a fine balance between the DNA methyltransferases (DNMTs) and DNA demethylases (TET family).

DNMT1, DNMT3A and DNMT3B use S-adenosyl-methionine (SAM) as methyl donor for the methyltransferase reaction. DNMT1 is responsible for maintenance of DNA methylation after its

synthesis and prefers hemi-methylated DNA as substrate [83]. DNMT3A and DNMT3B are, instead, *de novo* methyltransferases and methylate the DNA in different genomic positions. They display overlapping functions but DNMT3A is reported to be more active on naked DNA than DNMT3B; conversely DNMT3B prefers the DNA in the core nucleosome as substrate [84]. The reverse process of DNA demethylation is catalyzed by the TET (ten eleven translocation) protein family: TET1, TET2 and TET3 [85]. TET enzymes use alfa-ketoglutarate to oxidize 5-mC to 5-hydroxymethylcytosine (5-hmC), which can be further converted either to 5-formylcytosine or 5-carboxylcytosine [86]. These intermediate products are recognized by the base excision repairs system to substitute with an unmodified cytosine [85]. Mutations in DNMTs and TET enzymes is observed with a mutual exclusivity pattern in cancer (see **Figure**). Alteration of DNA methylation can affect cancer cells with at least three different mechanisms: *i)* general hypomethylation of cancer genome, leading to genomic instability; *ii)* focal hypermethylation of oncosuppressive genes; *iii)* direct mutagenetic effects of 5-mC by deamination.

BOX 2: Histone post-translational modifications and Nucleosome remodeling

Histones are basic proteins important for regulating many biological processes such as packaging of the DNA, access to the chromatin, gene expression and DNA repair. Similarly, to many other proteins, histones can undergo post-translational modifications (PTMs) as marks, which are added as chemical group to the tail and core of histone proteins. Better characterized histone PTMs are methylations, requiring SAM as methyl-donor, and acetylation that requires acetyl-CoA as acetyl-donor. Methylations and acetylation of lysines (more residues are the lysines 4, 9 and 27 of histone H3) are influencing chromatin condensation influencing transcriptional factor accessibility. Dysregulation of histone acetyltransferases (HATs), deacetylases (HDACs), methyltransferases (HMTs) and demethylases are found commonly altered in cancer (**Table 2**) and can represent determinants of the pathogenesis [87–102]. These group of enzymes have become common therapeutic targets in cancer for their potential to directly affect expression of oncogenes and oncosuppressors [103–106]. More recently “non canonical” modifications have also emerged, including acylation, lactylation, homocysteinylation, serotonylation, succinylation (see **Figure**). Central-carbon and one-carbon metabolism, ketogenesis, and redox balance supply the cell with the intermediates required to modulate addition/removal of histones PTMs. These in concert with DNA modifications, chromatin modifiers, remodellers and transcription factors impinge on the global transcriptional programme.

In addition to histone post-translational modifications and histone variants the fine regulation of the chromatin state is also mediated by structural remodeling of chromatin [107]. This is regulated by a group of defined ATP-dependent complexes, which regulate the chromatin accessibility by altering the position of nucleosomes. These complexes fall into four families: SWI/SNF, INO80, CHD and ISWI [108]. Briefly, SWI/SNF controls chromatin accessibility by nucleosome repositioning, ejection or histone dimer eviction. The complexes CHD and ISWI are mainly involved in the nucleosome assembly, maturation and spacing. Lastly, INO80 primarily installs and removes histone variants [107]. In the last decade, genome wide sequencing studies have shed light on the recurrence of mutations in this type of epigenetic regulators (**Table 3**). In particular, more than 20% of mutations described across different types of cancer belong to components of the SWI/SNF family [48], including SNF5 and ARID1A/B, while mutations in members of the INO80, CHD and ISWI families are less common [109].

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References

[1] I. Mihaylov, M. Kańduła, M. Krachunov, D. Vassilev, A novel framework for horizontal and vertical data integration in cancer studies with application to survival time prediction models, Biol. Direct. 14 (2019) 22–22. https://doi.org/10.1186/s13062-019-0249-6.

[2] Z.N. Harris, E. Dhungel, M. Mosior, T.H. Ahn, Massive metagenomic data analysis using abundance-based machine learning, Biol. Direct. 14 (2019) 12. https://doi.org/10.1186/s13062-019-0242-0.

[3] A. Chatterjee, E.J. Rodger, M.R. Eccles, Epigenetic drivers of tumourigenesis and cancer metastasis, Semin. Cancer Biol. 51 (2018) 149–159. https://doi.org/10.1016/j.semcancer.2017.08.004.

[4] D. Alonso-Curbelo, Y.-J. Ho, C. Burdziak, J. L. V. Maag, J.P.I. Morris, R. Chandwani, H.-A. Chen, K.M. Tsanov, F.M. Barriga, W. Luan, N. Tasdemir, G. Livshits, E. Azizi, J. Chun, J.E. Wilkinson, L. Mazutis, S.D. Leach, R. Koche, D. Pe'er, S.W. Lowe, A gene–environment-induced epigenetic program initiates tumorigenesis, Nature. (2021).

[5] E. Kadosh, I. Snir-Alkalay, A. Venkatachalam, S. May, A. Lasry, E. Elyada, A. Zinger, M. Shaham, G. Vaalani, M. Mernberger, T. Stiewe, E. Pikarsky, M. Oren, Y. Ben-Neriah, The gut microbiome switches mutant p53 from tumour-suppressive to oncogenic, Nature. 586 (2020) 133–138. https://doi.org/10.1038/s41586-020-2541-0.

[6] I. Celardo, G. Melino, I. Amelio, Commensal microbes and p53 in cancer progression, Biol. Direct. 15 (2020). https://doi.org/10.1186/s13062-020-00281-4.

[7] I. Amelio, M. Mancini, V. Petrova, R.A. Cairns, P. Vikhreva, S. Nicolai, A. Marini, A.A. Antonov, J. Le Quesne, J.D. Baena Acevedo, K. Dudek, G. Sozzi, U. Pastorino, R.A. Knight, T.W. Mak, G. Melino, p53 mutants cooperate with HIF-1 in transcriptional regulation of extracellular matrix components to promote tumor progression, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) E10869–E10878. https://doi.org/10.1073/pnas.1808314115.

[8] I. Amelio, R. Bertolo, P. Bove, O.C. Buonomo, E. Candi, M. Chiocchi, C. Cipriani, N. Di Daniele, C. Ganini, H. Juhl, A. Mauriello, C. Marani, J. Marshall, M. Montanaro, G. Palmieri, M. Piacentini, G. Sica, M. Tesauro, V. Rovella, G. Tisone, Y. Shi, Y. Wang, G. Melino, Liquid biopsies and cancer omics, Cell Death Discov. 6 (2020). https://doi.org/10.1038/s41420-020-00373-0.

[9] I. Amelio, G. Melino, Context is everything: extrinsic signalling and gain-of-function p53 mutants, Cell Death Discov. 6 (2020) 16. https://doi.org/10.1038/s41420-020-0251-x.

[10] M. Pieraccioli, S. Nicolai, C. Pitolli, M. Agostini, A. Antonov, M. Malewicz, R.A. Knight, G. Raschellá, G. Melino, ZNF281 inhibits neuronal differentiation and is a prognostic marker for neuroblastoma, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) 7356–7361. https://doi.org/10.1073/pnas.1801435115.

[11] C. Pitolli, Y. Wang, E. Candi, Y. Shi, G. Melino, I. Amelio, p53-Mediated Tumor Suppression: DNA-Damage Response and Alternative Mechanisms, Cancers (Basel). 11 (2019) 1983. https://doi.org/10.3390/cancers11121983.

[12] C. Pitolli, Y. Wang, M. Mancini, Y. Shi, G. Melino, I. Amelio, Do Mutations Turn p53 into an Oncogene?, Int. J. Mol. Sci. 20 (2019) 6241. https://doi.org/10.3390/ijms20246241.

[13] M.R. Corces, J.M. Granja, S. Shams, B.H. Louie, J.A. Seoane, W. Zhou, T.C. Silva, C. Groeneveld, C.K. Wong, S.W. Cho, A.T. Satpathy, M.R. Mumbach, K.A. Hoadley, A.G. Robertson, N.C. Sheffield, I. Felau, M.A.A. Castro, B.P. Berman, L.M. Staudt, J.C. Zenklusen, P.W. Laird, C. Curtis, W.J. Greenleaf, H.Y. Chang, The chromatin accessibility landscape of primary human cancers, Science (80-.). (2018). https://doi.org/10.1126/science.aav1898.

[14] W.A. Flavahan, E. Gaskell, B.E. Bernstein, Epigenetic plasticity and the hallmarks of cancer, Science (80-.). (2017). https://doi.org/10.1126/science.aal2380.

[15] H. Chen, C. Li, X. Peng, Z. Zhou, J.N. Weinstein, S.J. Caesar-Johnson, J.A. Demchok, I. Felau, M. Kasapi, M.L. Ferguson, C.M. Hutter, H.J. Sofia, R. Tarnuzzer, Z. Wang, L. Yang, J.C. Zenklusen, J. (Julia) Zhang, S. Chudamani, J. Liu, L. Lolla, R. Naresh, T. Pihl, Q. Sun, Y. Wan, Y. Wu, J. Cho, T. DeFreitas, S. Frazer, N. Gehlenborg, G. Getz, D.I. Heiman, J. Kim, M.S. Lawrence, P. Lin, S. Meier, M.S. Noble, G. Saksena, D. Voet, H. Zhang, B. Bernard, N. Chambwe, V. Dhankani, T. Knijnenburg, R. Kramer, K. Leinonen, Y. Liu, M.

Miller, S. Reynolds, I. Shmulevich, V. Thorsson, W. Zhang, R. Akbani, B.M. Broom, A.M. Hegde, Z. Ju, R.S. Kanchi, A. Korkut, J. Li, H. Liang, S. Ling, W. Liu, Y. Lu, G.B. Mills, K.S. Ng, A. Rao, M. Ryan, J. Wang, J.N. Weinstein, J. Zhang, A. Abeshouse, J. Armenia, D. Chakravarty, W.K. Chatila, I. de Bruijn, J. Gao, B.E. Gross, Z.J. Heins, R. Kundra, K. La, M. Ladanyi, A. Luna, M.G. Nissan, A. Ochoa, S.M. Phillips, E. Reznik, F. Sanchez-Vega, C. Sander, N. Schultz, R. Sheridan, S.O. Sumer, Y. Sun, B.S. Taylor, J. Wang, H. Zhang, P. Anur, M. Peto, P. Spellman, C. Benz, J.M. Stuart, C.K. Wong, C. Yau, D.N. Hayes, J.S. Parker, M.D. Wilkerson, A. Ally, M. Balasundaram, R. Bowlby, D. Brooks, R. Carlsen, E. Chuah, N. Dhalla, R. Holt, S.J.M. Jones, K. Kasaian, D. Lee, Y. Ma, M.A. Marra, M. Mayo, R.A. Moore, A.J. Mungall, K. Mungall, A.G. Robertson, S. Sadeghi, J.E. Schein, P. Sipahimalani, A. Tam, N. Thiessen, K. Tse, T. Wong, A.C. Berger, R. Beroukhim, A.D. Cherniack, C. Cibulskis, S.B. Gabriel, G.F. Gao, G. Ha, M. Meyerson, S.E. Schumacher, J. Shih, M.H. Kucherlapati, R.S. Kucherlapati, S. Baylin, L. Cope, L. Danilova, M.S. Bootwalla, P.H. Lai, D.T. Maglinte, D.J. Van Den Berg, D.J. Weisenberger, J.T. Auman, S. Balu, T. Bodenheimer, C. Fan, K.A. Hoadley, A.P. Hoyle, S.R. Jefferys, C.D. Jones, S. Meng, P.A. Mieczkowski, L.E. Mose, A.H. Perou, C.M. Perou, J. Roach, Y. Shi, J. V. Simons, T. Skelly, M.G. Soloway, D. Tan, U. Veluvolu, H. Fan, T. Hinoue, P.W. Laird, H. Shen, W. Zhou, M. Bellair, K. Chang, K. Covington, C.J. Creighton, H. Dinh, H.V. Doddapaneni, L.A. Donehower, J. Drummond, R.A. Gibbs, R. Glenn, W. Hale, Y. Han, J. Hu, V. Korchina, S. Lee, L. Lewis, W. Li, X. Liu, M. Morgan, D. Morton, D. Muzny, J. Santibanez, M. Sheth, E. Shinbrot, L. Wang, M. Wang, D.A. Wheeler, L. Xi, F. Zhao, J. Hess, E.L. Appelbaum, M. Bailey, M.G. Cordes, L. Ding, C.C. Fronick, L.A. Fulton, R.S. Fulton, C. Kandoth, E.R. Mardis, M.D. McLellan, C.A. Miller, H.K. Schmidt, R.K. Wilson, D. Crain, E. Curley, J. Gardner, K. Lau, D. Mallery, S. Morris, J. Paulauskis, R. Penny, C. Shelton, T. Shelton, M. Sherman, E. Thompson, P. Yena, J. Bowen, J.M. Gastier-Foster, M. Gerken, K.M. Leraas, T.M. Lichtenberg, N.C. Ramirez, L. Wise, E. Zmuda, N. Corcoran, T. Costello, C. Hovens, A.L. Carvalho, A.C. de Carvalho, J.H. Fregnani, A. Longatto-Filho, R.M. Reis, C. Scapulatempo-Neto, H.C.S. Silveira, D.O. Vidal, A. Burnette, J. Eschbacher, B. Hermes, A. Noss, R. Singh, M.L. Anderson, P.D. Castro, M. Ittmann, D. Huntsman, B. Kohl, X. Le, R. Thorp, C. Andry, E.R. Duffy, V. Lyadov, O. Paklina, G. Setdikova, A. Shabunin, M. Tavobilov, C. McPherson, R. Warnick, R. Berkowitz, D. Cramer, C. Feltmate, N. Horowitz, A. Kibel, M. Muto, C.P. Raut, A. Malykh, J.S. Barnholtz-Sloan, W. Barrett, K. Devine, J. Fulop, Q.T. Ostrom, K. Shimmel, Y. Wolinsky, A.E. Sloan, A. De Rose, F. Giuliante, M. Goodman, B.Y. Karlan, C.H. Hagedorn, J. Eckman, J. Harr, J. Myers, K. Tucker, L.A. Zach, B. Deyarmin, H. Hu, L. Kvecher, C. Larson, R.J. Mural, S. Somiari, A. Vicha, T. Zelinka, J. Bennett, M. Iacocca, B. Rabeno, P. Swanson, M. Latour, L. Lacombe, B. Têtu, A. Bergeron, M. McGraw, S.M. Staugaitis, J. Chabot, H. Hibshoosh, A. Sepulveda, T. Su, T. Wang, O. Potapova, O. Voronina, L. Desjardins, O. Mariani, S. Roman-Roman, X. Sastre, M.H. Stern, F. Cheng, S. Signoretti, A. Berchuck, D. Bigner, E. Lipp, J. Marks, S. McCall, R. McLendon, A. Secord, A. Sharp, M. Behera, D.J. Brat, A. Chen, K. Delman, S. Force, F. Khuri, K. Magliocca, S. Maithel, J.J. Olson, T. Owonikoko, A. Pickens, S. Ramalingam, D.M. Shin, G. Sica, E.G. Van Meir, H. Zhang, W. Eijckenboom, A. Gillis, E. Korpershoek, L. Looijenga, W. Oosterhuis, H. Stoop, K.E. van Kessel, E.C. Zwarthoff, C. Calatozzolo, L. Cuppini, S. Cuzzubbo, F. DiMeco, G. Finocchiaro, L. Mattei, A. Perin, B. Pollo, C. Chen, J. Houck, P. Lohavanichbutr, A. Hartmann, C. Stoehr, R. Stoehr, H. Taubert, S. Wach, B. Wullich, W. Kycler, D. Murawa, M. Wiznerowicz, K. Chung, W.J. Edenfield, J. Martin, E. Baudin, G. Bubley, R. Bueno, A. De Rienzo, W.G. Richards, S. Kalkanis, T. Mikkelsen, H. Noushmehr, L. Scarpace, N. Girard, M. Aymerich, E. Campo, E. Giné, A.L. Guillermo, N. Van Bang, P.T. Hanh, B.D. Phu, Y. Tang, H. Colman, K. Evason, P.R. Dottino, J.A. Martignetti, H. Gabra, H. Juhl, T. Akeredolu, S. Stepa, D. Hoon, K. Ahn, K.J. Kang, F. Beuschlein, A. Breggia, M. Birrer, D. Bell, M. Borad, A.H. Bryce, E. Castle, V. Chandan, J. Cheville, J.A. Copland, M. Farnell, T. Flotte, N. Giama, T. Ho, M. Kendrick, J.P. Kocher, K. Kopp, C. Moser, D. Nagorney, D. O'Brien, B.P. O'Neill, T. Patel, G. Petersen, F. Que, M. Rivera, L. Roberts, R. Smallridge, T. Smyrk, M. Stanton, R.H. Thompson, M. Torbenson, J.D. Yang, L. Zhang, F. Brimo, J.A. Ajani, A.M.A. Gonzalez, C. Behrens, J. Bondaruk, R. Broaddus, B. Czerniak, B. Esmaeli, J. Fujimoto, J. Gershenwald, C. Guo, A.J. Lazar, C. Logothetis, F. Meric-Bernstam,

C. Moran, L. Ramondetta, D. Rice, A. Sood, P. Tamboli, T. Thompson, P. Troncoso, A. Tsao, I. Wistuba, C. Carter, L. Haydu, P. Hersey, V. Jakrot, H. Kakavand, R. Kefford, K. Lee, G. Long, G. Mann, M. Quinn, R. Saw, R. Scolyer, K. Shannon, A. Spillane, J. Stretch, M. Synott, J. Thompson, J. Wilmott, H. Al-Ahmadie, T.A. Chan, R. Ghossein, A. Gopalan, D.A. Levine, V. Reuter, S. Singer, B. Singh, N.V. Tien, T. Broudy, C. Mirsaidi, P. Nair, P. Drwiega, J. Miller, J. Smith, H. Zaren, J.W. Park, N.P. Hung, E. Kebebew, W.M. Linehan, A.R. Metwalli, K. Pacak, P.A. Pinto, M. Schiffman, L.S. Schmidt, C.D. Vocke, N. Wentzensen, R. Worrell, H. Yang, M. Moncrieff, C. Goparaju, J. Melamed, H. Pass, N. Botnariuc, I. Caraman, M. Cernat, I. Chemencedji, A. Clipca, S. Doruc, G. Gorincioi, S. Mura, M. Pirtac, I. Stancul, D. Tcaciuc, M. Albert, I. Alexopoulou, A. Arnaout, J. Bartlett, J. Engel, S. Gilbert, J. Parfitt, H. Sekhon, G. Thomas, D.M. Rassl, R.C. Rintoul, C. Bifulco, R. Tamakawa, W. Urba, N. Hayward, H. Timmers, A. Antenucci, F. Facciolo, G. Grazi, M. Marino, R. Merola, R. de Krijger, A.P. Gimenez-Roqueplo, A. Piché, S. Chevalier, G. McKercher, K. Birsoy, G. Barnett, C. Brewer, C. Farver, T. Naska, N.A. Pennell, D. Raymond, C. Schilero, K. Smolenski, F. Williams, C. Morrison, J.A. Borgia, M.J. Liptay, M. Pool, C.W. Seder, K. Junker, L. Omberg, M. Dinkin, G. Manikhas, D. Alvaro, M.C. Bragazzi, V. Cardinale, G. Carpino, E. Gaudio, D. Chesla, S. Cottingham, M. Dubina, F. Moiseenko, R. Dhanasekaran, K.F. Becker, K.P. Janssen, J. Slotta-Huspenina, M.H. Abdel-Rahman, D. Aziz, S. Bell, C.M. Cebulla, A. Davis, R. Duell, J.B. Elder, J. Hilty, B. Kumar, J. Lang, N.L. Lehman, R. Mandt, P. Nguyen, R. Pilarski, K. Rai, L. Schoenfield, K. Senecal, P. Wakely, P. Hansen, R. Lechan, J. Powers, A. Tischler, W.E. Grizzle, K.C. Sexton, A. Kastl, J. Henderson, S. Porten, J. Waldmann, M. Fassnacht, S.L. Asa, D. Schadendorf, M. Couce, M. Graefen, H. Huland, G. Sauter, T. Schlomm, R. Simon, P. Tennstedt, O. Olabode, M. Nelson, O. Bathe, P.R. Carroll, J.M. Chan, P. Disaia, P. Glenn, R.K. Kelley, C.N. Landen, J. Phillips, M. Prados, J. Simko, K. Smith-McCune, S. VandenBerg, K. Roggin, A. Fehrenbach, A. Kendler, S. Sifri, R. Steele, A. Jimeno, F. Carey, I. Forgie, M. Mannelli, M. Carney, B. Hernandez, B. Campos, C. Herold-Mende, C. Jungk, A. Unterberg, A. von Deimling, A. Bossler, J. Galbraith, L. Jacobus, M. Knudson, T. Knutson, D. Ma, M. Milhem, R. Sigmund, A.K. Godwin, R. Madan, H.G. Rosenthal, C. Adebamowo, S.N. Adebamowo, A. Boussioutas, D. Beer, T. Giordano, A.M. Mes-Masson, F. Saad, T. Bocklage, L. Landrum, R. Mannel, K. Moore, K. Moxley, R. Postier, J. Walker, R. Zuna, M. Feldman, F. Valdivieso, R. Dhir, J. Luketich, E.M.M. Pinero, M. Quintero-Aguilo, C.G. Carlotti, J.S. Dos Santos, R. Kemp, A. Sankarankuty, D. Tirapelli, J. Catto, K. Agnew, E. Swisher, J. Creaney, B. Robinson, C.S. Shelley, E.M. Godwin, S. Kendall, C. Shipman, C. Bradford, T. Carey, A. Haddad, J. Moyer, L. Peterson, M. Prince, L. Rozek, G. Wolf, R. Bowman, K.M. Fong, I. Yang, R. Korst, W.K. Rathmell, J.L. Fantacone-Campbell, J.A. Hooke, A.J. Kovatich, C.D. Shriver, J. DiPersio, B. Drake, R. Govindan, S. Heath, T. Ley, B. Van Tine, P. Westervelt, M.A. Rubin, J. Il Lee, N.D. Aredes, A. Mariamidze, H. Liang, A Pan-Cancer Analysis of Enhancer Expression in Nearly 9000 Patient Samples, Cell. (2018). https://doi.org/10.1016/j.cell.2018.03.027.

[16] G. Della Chiara, F. Gervasoni, C. Godano, M. Fakiola, L. Azzolin, V. Ranzani, C. D'Oria, R.J.P. Bonnal, G. Moreni, M. De Simone, R. Bason, G. Rossetti, F. Panariello, F. Zanconato, M. Forcato, O. Romano, J. Caroli, L. Drufuca, P. Gruarin, V. Bevilacqua, M. Lorenzo, M.L. Sarnicola, M. Cordenonsi, M. Sandini, N. Zucchini, A. Pisani Ceretti, N. Mariani, A. Cassingena, A. Sartore-Bianchi, G. Testa, L. Gianotti, E. Opocher, G. Macino, S. Siena, S. Abrignani, S. Bicciato, S. Piccolo, M. Pagani, Epigenetic landscape of human colorectal cancer unveils an aberrant core of pan- cancer enhancers orchestrated by YAP/TAZ, Manuscr. Submitt. (2021). https://doi.org/10.1038/s41467-021-22544-y.

[17] I. Amelio, R. Bertolo, P. Bove, E. Candi, M. Chiocchi, C. Cipriani, N. Di Daniele, C. Ganini, H. Juhl, A. Mauriello, C. Marani, J. Marshall, M. Montanaro, G. Palmieri, M. Piacentini, G. Sica, M. Tesauro, V. Rovella, G. Tisone, Y. Shi, Y. Wang, G. Melino, Cancer predictive studies, Biol. Direct. 15 (2020). https://doi.org/10.1186/s13062-020-00274-3.

[18] D. Sturm, H. Witt, V. Hovestadt, D.A. Khuong-Quang, D.T.W. Jones, C. Konermann, E. Pfaff, M. Tönjes, M. Sill, S. Bender, M. Kool, M. Zapatka, N. Becker, M. Zucknick, T. Hielscher, X.Y. Liu, A.M. Fontebasso, M. Ryzhova, S. Albrecht, K. Jacob, M. Wolter, M. Ebinger, M.U. Schuhmann, T. van Meter, M.C. Frühwald, H. Hauch, A. Pekrun, B.

Radlwimmer, T. Niehues, G. Von Komorowski, M. Dürken, A.E. Kulozik, J. Madden, A. Donson, N.K. Foreman, R. Drissi, M. Fouladi, W. Scheurlen, A. von Deimling, C. Monoranu, W. Roggendorf, C. Herold-Mende, A. Unterberg, C.M. Kramm, J. Felsberg, C. Hartmann, B. Wiestler, W. Wick, T. Milde, O. Witt, A.M. Lindroth, J. Schwartzentruber, D. Faury, A. Fleming, M. Zakrzewska, P.P. Liberski, K. Zakrzewski, P. Hauser, M. Garami, A. Klekner, L. Bognar, S. Morrissy, F. Cavalli, M.D. Taylor, P. van Sluis, J. Koster, R. Versteeg, R. Volckmann, T. Mikkelsen, K. Aldape, G. Reifenberger, V.P. Collins, J. Majewski, A. Korshunov, P. Lichter, C. Plass, N. Jabado, S.M. Pfister, Hotspot Mutations in H3F3A and IDH1 Define Distinct Epigenetic and Biological Subgroups of Glioblastoma, Cancer Cell. (2012). https://doi.org/10.1016/j.ccr.2012.08.024.

[19] L. Bjerke, A. Mackay, M. Nandhabalan, A. Burford, A. Jury, S. Popov, D.A. Bax, D. Carvalho, K.R. Taylor, M. Vinci, I. Bajrami, I.M. McGonnell, C.J. Lord, R.M. Reis, D. Hargrave, A. Ashworth, P. Workman, C. Jones, Histone H3.3 mutations drive pediatric glioblastoma through upregulation of MYCN, Cancer Discov. (2013). https://doi.org/10.1158/2159-8290.CD-12-0426.

[20] K. Funato, V. Tabar, Histone Mutations in Cancer, Annu. Rev. Cancer Biol. (2018). https://doi.org/10.1146/annurev-cancerbio-030617-050143.

[21] S. Yang, X. Zheng, C. Lu, G.M. Li, C.D. Allis, H. Li, Molecular basis for oncohistone H3 recognition by SETD2 methyltransferase, Genes Dev. (2016). https://doi.org/10.1101/gad.284323.116.

[22] J. Okosun, C. Bödör, J. Wang, S. Araf, C.Y. Yang, C. Pan, S. Boller, D. Cittaro, M. Bozek, S. Iqbal, J. Matthews, D. Wrench, J. Marzec, K. Tawana, N. Popov, C. O'riain, D. O'shea, E. Carlotti, A. Davies, C.H. Lawrie, A. Matolcsy, M. Calaminici, A. Norton, R.J. Byers, C. Mein, E. Stupka, T.A. Lister, G. Lenz, S. Montoto, J.G. Gribben, Y. Fan, R. Grosschedl, C. Chelala, J. Fitzgibbon, Integrated genomic analysis identifies recurrent mutations and evolution patterns driving the initiation and progression of follicular lymphoma, Nat. Genet. 46 (2014) 176–181. https://doi.org/10.1038/ng.2856.

[23] N. Yusufova, A. Kloetgen, M. Teater, A. Osunsade, J.M. Camarillo, C.R. Chin, A.S. Doane, B.J. Venters, S. Portillo-Ledesma, J. Conway, J.M. Phillip, O. Elemento, D.W. Scott, W. Béguelin, J.D. Licht, N.L. Kelleher, L.M. Staudt, A.I. Skoultchi, M.C. Keogh, E. Apostolou, C.E. Mason, M. Imielinski, T. Schlick, Y. David, A. Tsirigos, C.D. Allis, A.A. Soshnev, E. Cesarman, A.M. Melnick, Histone H1 loss drives lymphoma by disrupting 3D chromatin architecture, Nature. 589 (2021) 299–305. https://doi.org/10.1038/s41586-020-3017-y.

[24] M.A. Willcockson, S.E. Healton, C.N. Weiss, B.A. Bartholdy, Y. Botbol, L.N. Mishra, D.S. Sidhwani, T.J. Wilson, H.B. Pinto, M.I. Maron, K.A. Skalina, L.N. Toro, J. Zhao, C.H. Lee, H. Hou, N. Yusufova, C. Meydan, A. Osunsade, Y. David, E. Cesarman, A.M. Melnick, S. Sidoli, B.A. Garcia, W. Edelmann, F. Macian, A.I. Skoultchi, H1 histones control the epigenetic landscape by local chromatin compaction, Nature. 589 (2021) 293–298. https://doi.org/10.1038/s41586-020-3032-z.

[25] R.L. Bennett, A. Bele, E.C. Small, C.M. Will, B. Nabet, J.A. Oyer, X. Huang, R.P. Ghosh, A.T. Grzybowski, T. Yu, Q. Zhang, A. Riva, T.P. Lele, G.C. Schatz, N.L. Kelleher, A.J. Ruthenburg, J. Liphardt, J.D. Licht, A mutation in histone H2B represents a new class of oncogenic driver, Cancer Discov. (2019). https://doi.org/10.1158/2159-8290.CD-19-0393.

[26] G.-L. Chew, M. Bleakley, R.K. Bradley, H.S. Malik, S. Henikoff, A. Molaro, J. Sarthy, Short H2A histone variants are expressed in cancer, Nat. Commun. (2021).

[27] D. Vassiliadis, M.A. Dawson, Mutation alters chromatin changes during injury response to drive cancer, Nature. 590 (2021). https://doi.org/10.1038/d41586-021-00211-y.

[28] M. Chierici, M. Francescatto, N. Bussola, G. Jurman, C. Furlanello, Predictability of drug-induced liver injury by machine learning, Biol. Direct. 15 (2020) 3. https://doi.org/10.1186/s13062-020-0259-4.

[29] G.R. Sumsion, M.S. Bradshaw, J.T. Beales, E. Ford, G.R.G. Caryotakis, D.J. Garrett, E.D. Lebaron, I.O. Nwosu, S.R. Piccolo, Diverse approaches to predicting drug-induced liver injury using gene-expression profiles, Biol. Direct. 15 (2020). https://doi.org/10.1186/s13062-019-0257-6.

[30] N. Yosef, A. Regev, Writ large: Genomic dissection of the effect of cellular environment on immune response, Science (80-.). 354 (2016) 64–68.

https://doi.org/10.1126/science.aaf5453.
[31] J. Kawulok, M. Kawulok, S. Deorowicz, Environmental metagenome classification for constructing a microbiome fingerprint, Biol. Direct. 14 (2019). https://doi.org/10.1186/s13062-019-0251-z.
[32] C.S. Casimiro-Soriguer, C. Loucera, J. Perez Florido, D. López-López, J. Dopazo, Antibiotic resistance and metabolic profiles as functional biomarkers that accurately predict the geographic origin of city metagenomics samples, Biol. Direct. 14 (2019) 15–15. https://doi.org/10.1186/s13062-019-0246-9.
[33] Q. Zheng, N.A. Prescott, I. Maksimovic, Y. David, (De)Toxifying the Epigenetic Code, Chem. Res. Toxicol. 32 (2019) 796–807. https://doi.org/10.1021/acs.chemrestox.9b00013.
[34] S. Melino, R. Sabelli, M. Paci, Allyl sulfur compounds and cellular detoxification system: Effects and perspectives in cancer therapy, Amino Acids. 41 (2011) 103–112. https://doi.org/10.1007/s00726-010-0522-6.
[35] Á. García-Guede, O. Vera, I. Ibáñez-de-Caceres, When oxidative stress meets epigenetics: Implications in cancer development, Antioxidants. 9 (2020) 1–26. https://doi.org/10.3390/antiox9060468.
[36] X. Wu, Y. Zhang, TET-mediated active DNA demethylation: Mechanism, function and beyond, Nat. Rev. Genet. 18 (2017) 517–534. https://doi.org/10.1038/nrg.2017.33.
[37] S. Kreuz, W. Fischle, Oxidative stress signaling to chromatin in health and disease, Epigenomics. 8 (2016) 843–862. https://doi.org/10.2217/epi-2016-0002.
[38] R. Nepravishta, R. Sabelli, E. Iorio, L. Micheli, M. Paci, S. Melino, Oxidative species and S-glutathionyl conjugates in the apoptosis induction by allyl thiosulfate, FEBS J. 279 (2012) 154–167. https://doi.org/10.1111/j.1742-4658.2011.08407.x.
[39] T. Cabras, M. Patamia, S. Melino, R. Inzitari, I. Messana, M. Castagnola, R. Petruzzelli, Pro-oxidant activity of histatin 5 related Cu(II)-model peptide probed by mass spectrometry, Biochem. Biophys. Res. Commun. 358 (2007) 277–284. https://doi.org/10.1016/j.bbrc.2007.04.121.
[40] M. Batie, J. Frost, M. Frost, J.W. Wilson, P. Schofield, S. Rocha, Hypoxia induces rapid changes to histone methylation reprogramming chromatin for the cellular response, Science (80-.). 1226 (2019) 1222–1226. https://doi.org/10.1101/513069.
[41] A.A. Chakraborty, T. Laukka, M. Myllykoski, A.E. Ringel, M.A. Booker, M.Y. Tolstorukov, Y.J. Meng, S.R. Meier, R.B. Jennings, A.L. Creech, Z.T. Herbert, S.K. McBrayer, B.A. Olenchock, J.D. Jaffe, M.C. Haigis, R. Beroukhim, S. Signoretti, P. Koivunen, W.G. Kaelin, Histone demethylase KDM6A directly senses oxygen to control chromatin and cell fate, Science (80-.). 363 (2019) 1217–1222. https://doi.org/10.1126/science.aaw1026.
[42] C. Rinaldi, P. Pizzul, M.P. Longhese, D. Bonetti, Sensing R-Loop-Associated DNA Damage to Safeguard Genome Stability, Front. Cell Dev. Biol. (2021). https://doi.org/10.3389/fcell.2020.618157.
[43] M. Berdasco, M. Esteller, Aberrant Epigenetic Landscape in Cancer: How Cellular Identity Goes Awry, Dev. Cell. (2010). https://doi.org/10.1016/j.devcel.2010.10.005.
[44] N.P. Dantuma, H. Attikum, Spatiotemporal regulation of posttranslational modifications in the DNA damage response , EMBO J. (2016). https://doi.org/10.15252/embj.201592595.
[45] J.H.A. Vissers, M. Van Lohuizen, E. Citterio, The emerging role of Polycomb repressors in the response to DNA damage, J. Cell Sci. (2012). https://doi.org/10.1242/jcs.107375.
[46] M. Alagoz, Y. Katsuki, H. Ogiwara, T. Ogi, A. Shibata, A. Kakarougkas, P. Jeggo, SETDB1, HP1 and SUV39 promote repositioning of 53BP1 to extend resection during homologous recombination in G2 cells, Nucleic Acids Res. (2015). https://doi.org/10.1093/nar/gkv722.
[47] Y. Park, M.H. Chui, Y.S. Rahmanto, Z.C. Yu, R.A. Shamanna, M.A. Bellani, S. Gaillard, A. Ayhan, A. Viswanathan, M.M. Seidman, S. Franco, A.K.L. Leung, V.A. Bohr, I.M. Shih, T.L. Wang, Loss of ARID1A in tumor cells renders selective vulnerability to combined ionizing radiation and PARP inhibitor therapy, Clin. Cancer Res. (2019). https://doi.org/10.1158/1078-0432.CCR-18-4222.
[48] P. Mittal, C.W.M. Roberts, The SWI/SNF complex in cancer — biology, biomarkers and therapy, Nat. Rev. Clin. Oncol. (2020). https://doi.org/10.1038/s41571-020-0357-3.
[49] M.K. Konkel, M.A. Batzer, A mobile threat to genome stability: The impact of non-LTR retrotransposons upon the human genome, Semin. Cancer Biol. 20 (2010) 211–221.

https://doi.org/10.1016/j.semcancer.2010.03.001.
[50] J.Z. Shen, Z. Qiu, Q. Wu, D. Finlay, G. Garcia, D. Sun, J. Rantala, W. Barshop, J.L. Hope, R.C. Gimple, O. Sangfelt, L.M. Bradley, J. Wohlschlegel, J.N. Rich, C. Spruck, FBXO44 promotes DNA replication-coupled repetitive element silencing in cancer cells, Cell. 184 (2021) 352-369.e23. https://doi.org/10.1016/j.cell.2020.11.042.
[51] T. García-Muse, A. Aguilera, R Loops: From Physiological to Pathological Roles, Cell. (2019). https://doi.org/10.1016/j.cell.2019.08.055.
[52] P.C. Stirling, P. Hieter, Canonical DNA Repair Pathways Influence R-Loop-Driven Genome Instability, J. Mol. Biol. (2017). https://doi.org/10.1016/j.jmb.2016.07.014.
[53] L.A. Sanz, S.R. Hartono, Y.W. Lim, S. Steyaert, A. Rajpurkar, P.A. Ginno, X. Xu, F. Chédin, Prevalent, Dynamic, and Conserved R-Loop Structures Associate with Specific Epigenomic Signatures in Mammals, Mol. Cell. (2016). https://doi.org/10.1016/j.molcel.2016.05.032.
[54] L. Wahba, L. Costantino, F.J. Tan, A. Zimmer, D. Koshland, S1-DRIP-seq identifies high expression and polyA tracts as major contributors to R-loop formation, Genes Dev. (2016). https://doi.org/10.1101/gad.280834.116.
[55] M.P. Crossley, M. Bocek, K.A. Cimprich, R-Loops as Cellular Regulators and Genomic Threats, Mol. Cell. (2019). https://doi.org/10.1016/j.molcel.2019.01.024.
[56] P.A. Ginno, P.L. Lott, H.C. Christensen, I. Korf, F. Chédin, R-Loop Formation Is a Distinctive Characteristic of Unmethylated Human CpG Island Promoters, Mol. Cell. (2012). https://doi.org/10.1016/j.molcel.2012.01.017.
[57] C. Grunseich, I.X. Wang, J.A. Watts, J.T. Burdick, R.D. Guber, Z. Zhu, A. Bruzel, T. Lanman, K. Chen, A.B. Schindler, N. Edwards, A. Ray-Chaudhury, J. Yao, T. Lehky, G. Piszczek, B. Crain, K.H. Fischbeck, V.G. Cheung, Senataxin Mutation Reveals How R-Loops Promote Transcription by Blocking DNA Methylation at Gene Promoters, Mol. Cell. (2018). https://doi.org/10.1016/j.molcel.2017.12.030.
[58] P.B. Chen, H. V. Chen, D. Acharya, O.J. Rando, T.G. Fazzio, R loops regulate promoter-proximal chromatin architecture and cellular differentiation, Nat. Struct. Mol. Biol. (2015). https://doi.org/10.1038/nsmb.3122.
[59] A. Aguilera, T. García-Muse, R Loops: From Transcription Byproducts to Threats to Genome Stability, Mol. Cell. (2012). https://doi.org/10.1016/j.molcel.2012.04.009.
[60] P. Zeller, J. Padeken, R. Van Schendel, V. Kalck, M. Tijsterman, S.M. Gasser, Histone H3K9 methylation is dispensable for Caenorhabditis elegans development but suppresses RNA:DNA hybrid-associated repeat instability, Nat. Genet. 48 (2016) 1385–1395. https://doi.org/10.1038/ng.3672.
[61] B. Rodriguez-Martin, E.G. Alvarez, A. Baez-Ortega, J. Zamora, F. Supek, J. Demeulemeester, M. Santamarina, Y.S. Ju, J. Temes, D. Garcia-Souto, H. Detering, Y. Li, J. Rodriguez-Castro, A. Dueso-Barroso, A.L. Bruzos, S.C. Dentro, M.G. Blanco, G. Contino, D. Ardeljan, M. Tojo, N.D. Roberts, S. Zumalave, P.A.W. Edwards, J. Weischenfeldt, M. Puiggròs, Z. Chong, K. Chen, E.A. Lee, J.A. Wala, K. Raine, A. Butler, S.M. Waszak, F.C.P. Navarro, S.E. Schumacher, J. Monlong, F. Maura, N. Bolli, G. Bourque, M. Gerstein, P.J. Park, D.C. Wedge, R. Beroukhim, D. Torrents, J.O. Korbel, I. Martincorena, R.C. Fitzgerald, P. Van Loo, H.H. Kazazian, K.H. Burns, K.C. Akdemir, E.G. Alvarez, A. Baez-Ortega, R. Beroukhim, P.C. Boutros, D.D.L. Bowtell, B. Brors, K.H. Burns, P.J. Campbell, K. Chan, I. Cortés-Ciriano, A. Dueso-Barroso, A.J. Dunford, P.A. Edwards, X. Estivill, D. Etemadmoghadam, L. Feuerbach, J.L. Fink, M. Frenkel-Morgenstern, D.W. Garsed, M. Gerstein, D.A. Gordenin, D. Haan, J.E. Haber, J.M. Hess, B. Hutter, M. Imielinski, D.T.W. Jones, Y.S. Ju, M.D. Kazanov, L.J. Klimczak, Y. Koh, J.O. Korbel, K. Kumar, E.A. Lee, J.J.K. Lee, Y. Li, A.G. Lynch, G. Macintyre, F. Markowetz, I. Martincorena, A. Martinez-Fundichely, M. Meyerson, S. Miyano, H. Nakagawa, F.C.P. Navarro, S. Ossowski, J. V. Pearson, M. Puiggròs, K. Rippe, N.D. Roberts, S.A. Roberts, B. Rodriguez-Martin, S.E. Schumacher, R. Scully, M. Shackleton, N. Sidiropoulos, L. Sieverling, C. Stewart, J.M.C. Tubio, I. Villasante, N. Waddell, J.A. Wala, J. Weischenfeldt, L. Yang, X. Yao, S.S. Yoon, J. Zamora, C.Z. Zhang, P.J. Campbell, J.M.C. Tubio, Pan-cancer analysis of whole genomes identifies driver rearrangements promoted by LINE-1 retrotransposition, Nat. Genet. 52 (2020) 306–319. https://doi.org/10.1038/s41588-019-0562-0.
[62] A. Mainieri, D. Haig, Retrotransposon gag-like 1 (RTL1) and the molecular evolution of self-

targeting imprinted microRNAs, Biol. Direct. 14 (2019). https://doi.org/10.1186/s13062-019-0250-0.
[63] V. Bhatia, S.I. Barroso, M.L. García-Rubio, E. Tumini, E. Herrera-Moyano, A. Aguilera, BRCA2 prevents R-loop accumulation and associates with TREX-2 mRNA export factor PCID2, Nature. (2014). https://doi.org/10.1038/nature13374.
[64] E. Hatchi, K. Skourti-Stathaki, S. Ventz, L. Pinello, A. Yen, K. Kamieniarz-Gdula, S. Dimitrov, S. Pathania, K.M. McKinney, M.L. Eaton, M. Kellis, S.J. Hill, G. Parmigiani, N.J. Proudfoot, D.M. Livingston, BRCA1 recruitment to transcriptional pause sites is required for R-loop-driven DNA damage repair, Mol. Cell. (2015). https://doi.org/10.1016/j.molcel.2015.01.011.
[65] M.L. García-Rubio, C. Pérez-Calero, S.I. Barroso, E. Tumini, E. Herrera-Moyano, I. V. Rosado, A. Aguilera, The Fanconi Anemia Pathway Protects Genome Integrity from R-loops, PLoS Genet. (2015). https://doi.org/10.1371/journal.pgen.1005674.
[66] W. Timp, A.P. Feinberg, Cancer as a dysregulated epigenome allowing cellular growth advantage at the expense of the host, Nat. Rev. Cancer. (2013). https://doi.org/10.1038/nrc3486.
[67] A. Sparmann, M. Van Lohuizen, Polycomb silencers control cell fate, development and cancer, Nat. Rev. Cancer. (2006). https://doi.org/10.1038/nrc1991.
[68] A.H. Shih, O. Abdel-Wahab, J.P. Patel, R.L. Levine, The role of mutations in epigenetic regulators in myeloid malignancies, Nat. Rev. Cancer. (2012). https://doi.org/10.1038/nrc3343.
[69] A.M. Pietersen, M. van Lohuizen, Stem cell regulation by polycomb repressors: postponing commitment, Curr. Opin. Cell Biol. (2008). https://doi.org/10.1016/j.ceb.2008.01.004.
[70] C.L. Scott, J. Gil, E. Hernando, J. Teruya-Feldstein, M. Narita, D. Martínez, T. Visakorpi, D. Mu, C. Cordon-Cardo, G. Peters, D. Beach, S.W. Lowe, Role of the chromobox protein CBX7 in lymphomagenesis, Proc. Natl. Acad. Sci. U. S. A. (2007). https://doi.org/10.1073/pnas.0608721104.
[71] C. Calés, M. Román-Trufero, L. Pavón, I. Serrano, T. Melgar, M. Endoh, C. Pérez, H. Koseki, M. Vidal, Inactivation of the Polycomb Group Protein Ring1B Unveils an Antiproliferative Role in Hematopoietic Cell Expansion and Cooperation with Tumorigenesis Associated with Ink4a Deletion, Mol. Cell. Biol. (2008). https://doi.org/10.1128/mcb.01136-07.
[72] H.R. Siddique, M. Saleem, Concise review: Role of BMI1, a stem cell factor, in cancer recurrence and chemoresistance: Preclinical and clinical evidences, Stem Cells. (2012). https://doi.org/10.1002/stem.1035.
[73] J.J.L. Jacobs, B. Scheijen, J.W. Voncken, K. Kieboom, A. Berns, M. Van Lohuizen, Bmi-1 collaborates with c-Myc in tumorigenesis by inhibiting c-Myc- induced apoptosis via INK4a/ARF, Genes Dev. (1999). https://doi.org/10.1101/gad.13.20.2678.
[74] Y. Haupt, M.L. Bath, A.W. Harris, J.M. Adams, bmi-1 transgene induces lymphomas and collaborates with myc in tumorigenesis, Oncogene. (1993).
[75] M.A. Maynard, R. Ferretti, K.I. Hilgendorf, C. Perret, P. Whyte, J.A. Lees, Bmi1 is required for tumorigenesis in a mouse model of intestinal cancer, Oncogene. (2014). https://doi.org/10.1038/onc.2013.333.
[76] C. Simon, J. Chagraoui, J. Krosl, P. Gendron, B. Wilhelm, S. Lemieux, G. Boucher, P. Chagnon, S. Drouin, R. Lambert, C. Rondeau, A. Bilodeau, S. Lavallée, M. Sauvageau, J. Hébert, G. Sauvageau, A key role for EZH2 and associated genes in mouse and human adult T-cell acute leukemia, Genes Dev. (2012). https://doi.org/10.1101/gad.186411.111.
[77] M. Mochizuki-Kashio, K. Aoyama, G. Sashida, M. Oshima, T. Tomioka, T. Muto, C. Wang, A. Iwama, Ezh2 loss in hematopoietic stem cells predisposes mice to develop heterogeneous malignancies in an Ezh1-dependent manner, Blood. (2015). https://doi.org/10.1182/blood-2015-03-634428.
[78] A. Herrera-Merchan, L. Arranz, J.M. Ligos, A. De Molina, O. Dominguez, S. Gonzalez, Ectopic expression of the histone methyltransferase Ezh2 in haematopoietic stem cells causes myeloproliferative disease, Nat. Commun. (2012). https://doi.org/10.1038/ncomms1623.
[79] T. Berg, S. Thoene, D. Yap, T. Wee, N. Schoeler, P. Rosten, E. Lim, M. Bilenky, A.J.

Mungall, T. Oellerich, S. Lee, C.K. Lai, P. Umlandt, A. Salmi, H. Chang, L. Yue, D. Lai, S.W.G. Cheng, R.D. Morin, M. Hirst, H. Serve, M.A. Marra, G.B. Morin, R.D. Gascoyne, S.A. Aparicio, R.K. Humphries, A transgenic mouse model demonstrating the oncogenic role of mutations in the polycomb-group gene EZH2 in lymphomagenesis, Blood. (2014). https://doi.org/10.1182/blood-2012-12-473439.

[80] X. Li, M.E. Gonzalez, K. Toy, T. Filzen, S.D. Merajver, C.G. Kleer, Targeted overexpression of EZH2 in the mammary gland disrupts ductal morphogenesis and causes epithelial hyperplasia, Am. J. Pathol. (2009). https://doi.org/10.2353/ajpath.2009.090042.

[81] J. Zhang, C. Yang, C. Wu, W. Cui, L. Wang, DNA methyltransferases in cancer: Biology, paradox, aberrations, and targeted therapy, Cancers (Basel). (2020). https://doi.org/10.3390/cancers12082123.

[82] P.A. Jones, Functions of DNA methylation: Islands, start sites, gene bodies and beyond, Nat. Rev. Genet. (2012). https://doi.org/10.1038/nrg3230.

[83] P. Bashtrykov, G. Jankevicius, A. Smarandache, R.Z. Jurkowska, S. Ragozin, A. Jeltsch, Specificity of dnmt1 for methylation of hemimethylated CpG sites resides in its catalytic domain, Chem. Biol. (2012). https://doi.org/10.1016/j.chembiol.2012.03.010.

[84] H. Takeshima, I. Suetake, H. Shimahara, K. Ura, S.I. Tate, S. Tajima, Distinct DNA methylation activity of Dnmt3a and Dnmt3b towards naked and nucleosomal DNA, J. Biochem. (2006). https://doi.org/10.1093/jb/mvj044.

[85] Y.F. He, B.Z. Li, Z. Li, P. Liu, Y. Wang, Q. Tang, J. Ding, Y. Jia, Z. Chen, N. Li, Y. Sun, X. Li, Q. Dai, C.X. Song, K. Zhang, C. He, G.L. Xu, Tet-mediated formation of 5-carboxylcytosine and its excision by TDG in mammalian DNA, Science (80-.). (2011). https://doi.org/10.1126/science.1210944.

[86] S. Ito, L. Shen, Q. Dai, S.C. Wu, L.B. Collins, J.A. Swenberg, C. He, Y. Zhang, Tet proteins can convert 5-methylcytosine to 5-formylcytosine and 5-carboxylcytosine, Science (80-.). (2011). https://doi.org/10.1126/science.1210597.

[87] H. Wu, P. Fan, J. Zhao, Z. Meng, H. Wu, B. Wang, X. Jin, Overexpressed histone acetyltransferase 1 regulates cancer immunity by increasing programmed death-ligand 1 expression in pancreatic cancer, J. Exp. Clin. Cancer Res. (2019). https://doi.org/10.1186/s13046-019-1044-z.

[88] B.P. Miao, R.S. Zhang, G. Yang, J.J. Sun, Y.Y. Tang, W.F. Liang, T. Liu, Z. Wen, P.C. Yang, G.H. Nie, Histone acetyltransferase 1 up regulates Bcl2L12 expression in nasopharyngeal cancer cells, Arch. Biochem. Biophys. (2018). https://doi.org/10.1016/j.abb.2018.03.040.

[89] G. Sashida, H. Harada, H. Matsui, M. Oshima, M. Yui, Y. Harada, S. Tanaka, M. Mochizuki-Kashio, C. Wang, A. Saraya, T. Muto, Y. Hayashi, K. Suzuki, H. Nakajima, T. Inaba, H. Koseki, G. Huang, T. Kitamura, A. Iwama, Ezh2 loss promotes development of myelodysplastic syndrome but attenuates its predisposition to leukaemic transformation, Nat. Commun. (2014). https://doi.org/10.1038/ncomms5177.

[90] P. Ntziachristos, A. Tsirigos, P. Van Vlierberghe, J. Nedjic, T. Trimarchi, M.S. Flaherty, D. Ferres-Marco, V. Da Ros, Z. Tang, J. Siegle, P. Asp, M. Hadler, I. Rigo, K. De Keersmaecker, J. Patel, T. Huynh, F. Utro, S. Poglio, J.B. Samon, E. Paietta, J. Racevskis, J.M. Rowe, R. Rabadan, R.L. Levine, S. Brown, F. Pflumio, M. Dominguez, A. Ferrando, I. Aifantis, Genetic inactivation of the polycomb repressive complex 2 in T cell acute lymphoblastic leukemia, Nat. Med. (2012). https://doi.org/10.1038/nm.2651.

[91] Y.F. Wang, J. Zhang, Y. Su, Y.Y. Shen, D.X. Jiang, Y.Y. Hou, M.Y. Geng, J. Ding, Y. Chen, G9a regulates breast cancer growth by modulating iron homeostasis through the repression of ferroxidase hephaestin, Nat. Commun. (2017). https://doi.org/10.1038/s41467-017-00350-9.

[92] C. Segovia, E. San José-Enériz, E. Munera-Maravilla, M. Martínez-Fernández, L. Garate, E. Miranda, A. Vilas-Zornoza, I. Lodewijk, C. Rubio, C. Segrelles, L.V. Valcárcel, O. Rabal, N. Casares, A. Bernardini, C. Suarez-Cabrera, F.F. López-Calderón, P. Fortes, J.A. Casado, M. Dueñas, F. Villacampa, J.J. Lasarte, F. Guerrero-Ramos, G. de Velasco, J. Oyarzabal, D. Castellano, X. Agirre, F. Prósper, J.M. Paramio, Inhibition of a G9a/DNMT network triggers immune-mediated bladder cancer regression, Nat. Med. (2019). https://doi.org/10.1038/s41591-019-0499-y.

[93] Y.C. Chae, J.Y. Kim, J.W. Park, K.B. Kim, H. Oh, K.H. Lee, S.B. Seo, FOXO1 degradation via G9a-mediated methylation promotes cell proliferation in colon cancer, Nucleic Acids Res. (2019). https://doi.org/10.1093/nar/gky1230.
[94] B. Majello, F. Gorini, C.D. Saccà, S. Amente, Expanding the role of the histone lysine-specific demethylase lsd1 in cancer, Cancers (Basel). (2019). https://doi.org/10.3390/cancers11030324.
[95] Y.F. Chen, R.Z. Luo, Y. Li, B.K. Cui, M. Song, A.K. Yang, W.K. Chen, High expression levels of COX-2 and P300 are associated with unfavorable survival in laryngeal squamous cell carcinoma, Eur. Arch. Oto-Rhino-Laryngology. (2013). https://doi.org/10.1007/s00405-012-2275-1.
[96] R. Dutta, B. Tiu, K.M. Sakamoto, CBP/p300 acetyltransferase activity in hematologic malignancies, Mol. Genet. Metab. (2016). https://doi.org/10.1016/j.ymgme.2016.06.013.
[97] Y. Li, E. Seto, HDACs and HDAC inhibitors in cancer development and therapy, Cold Spring Harb. Perspect. Med. (2016). https://doi.org/10.1101/cshperspect.a026831.
[98] R. Vatapalli, V. Sagar, Y. Rodriguez, J.C. Zhao, K. Unno, S. Pamarthy, B. Lysy, J. Anker, H. Han, Y.A. Yoo, M. Truica, Z.R. Chalmers, F. Giles, J. Yu, D. Chakravarti, B. Carneiro, S.A. Abdulkadir, Histone methyltransferase DOT1L coordinates AR and MYC stability in prostate cancer, Nat. Commun. (2020). https://doi.org/10.1038/s41467-020-18013-7.
[99] B. Zhu, S. Chen, H. Wang, C. Yin, C. Han, C. Peng, Z. Liu, L. Wan, X. Zhang, J. Zhang, C.G. Lian, P. Ma, Z.X. Xu, S. Prince, T. Wang, X. Gao, Y. Shi, D. Liu, M. Liu, W. Wei, Z. Wei, J. Pan, Y. Wang, Z. Xuan, J. Hess, N.K. Hayward, C.R. Goding, X. Chen, J. Zhou, R. Cui, The protective role of DOT1L in UV-induced melanomagenesis, Nat. Commun. (2018). https://doi.org/10.1038/s41467-017-02687-7.
[100] K. Xu, Z.J. Wu, A.C. Groner, H.H. He, C. Cai, R.T. Lis, X. Wu, E.C. Stack, M. Loda, T. Liu, H. Xu, L. Cato, J.E. Thornton, R.I. Gregory, C. Morrissey, R.L. Vessella, R. Montironi, C. Magi-Galluzzi, P.W. Kantoff, S.P. Balk, X.S. Liu, M. Brown, EZH2 Oncogenic Activity in Castration-Resistant Prostate Cancer Cells Is Polycomb-Independent, Science (80-.). (2012). https://doi.org/10.1126/science.1227604.
[101] D. Zingg, J. Debbache, S.M. Schaefer, E. Tuncer, S.C. Frommel, P. Cheng, N. Arenas-Ramirez, J. Haeusel, Y. Zhang, M. Bonalli, M.T. McCabe, C.L. Creasy, M.P. Levesque, O. Boyman, R. Santoro, O. Shakhova, R. Dummer, L. Sommer, The epigenetic modifier EZH2 controls melanoma growth and metastasis through silencing of distinct tumour suppressors, Nat. Commun. (2015). https://doi.org/10.1038/ncomms7051.
[102] M. Caganova, C. Carrisi, G. Varano, F. Mainoldi, F. Zanardi, P.L. Germain, L. George, F. Alberghini, L. Ferrarini, A.K. Talukder, M. Ponzoni, G. Testa, T. Nojima, C. Doglioni, D. Kitamura, K.M. Toellner, I.H. Su, S. Casola, Germinal center dysregulation by histone methyltransferase EZH2 promotes lymphomagenesis, J. Clin. Invest. (2013). https://doi.org/10.1172/JCI70626.
[103] S.E. Bates, Epigenetic Therapies for Cancer, N. Engl. J. Med. 383 (2020) 650–663. https://doi.org/10.1056/nejmra1805035.
[104] R.W. Johnstone, Histone-deacetylase inhibitors: Novel drugs for the treatment of cancer, Nat. Rev. Drug Discov. 1 (2002) 287–299. https://doi.org/10.1038/nrd772.
[105] R. Nepravishta, A. Bellomaria, F. Polizio, M. Paci, S. Melino, Reticulon RTN1-CCT peptide: A potential nuclease and inhibitor of histone deacetylase enzymes, Biochemistry. 49 (2010) 252–258. https://doi.org/10.1021/bi9012676.
[106] S. Melino, R. Nepravishta, A. Bellomaria, S. Di Marco, M. Paci, Nucleic acid binding of the RTN1-C C-terminal region: Toward the functional role of a reticulon protein, Biochemistry. 48 (2009) 242–253. https://doi.org/10.1021/bi801407w.
[107] C.R. Clapier, J. Iwasa, B.R. Cairns, C.L. Peterson, Mechanisms of action and regulation of ATP-dependent chromatin-remodelling complexes, Nat. Rev. Mol. Cell Biol. (2017). https://doi.org/10.1038/nrm.2017.26.
[108] D.J. Gaffney, G. McVicker, A.A. Pai, Y.N. Fondufe-Mittendorf, N. Lewellen, K. Michelini, J. Widom, Y. Gilad, J.K. Pritchard, Controls of Nucleosome Positioning in the Human Genome, PLoS Genet. (2012). https://doi.org/10.1371/journal.pgen.1003036.
[109] B. Zhou, L. Wang, S. Zhang, B.D. Bennett, F. He, Y. Zhang, C. Xiong, L. Han, L. Diao, P. Li, D.C. Fargo, A.D. Cox, G. Hu, INO80 governs superenhancer-mediated oncogenic

transcription and tumor growth in melanoma, Genes Dev. (2016). https://doi.org/10.1101/gad.277178.115.

Figure Legends

Figure 1. Mutational status of epigenetic regulators in cancer. Oncoprint for different classes of epigenetic factors showing the type and frequency of mutations observed in cancer. From cBioPortal database for Cancer Genomics TCGA PanCancer Altas (n= 10967) (https://www.cbioportal.org).

Figure 2. Role of FBXO44 in the maintenance of genome integrity. FBXO44 facilitates recruitment of SUV39H1, CRL4 and NuRD at the replication fork by binding H3K9me3-modified nucleosomes. This mechanism produces inhibition of repetitive elements (REs). In FBXO44 deficient cells, loss of the repressive mark H3K9me3 is observed, with a consequent increase of replication stress and DNA damage. Derepression of REs also triggers the formation of double-strand RNA (dsRNA) and activation of dsRNA cytosolic sensors (STING, MAVS) which, in turn, stimulate the antiviral pathways in cancer cells.

Sample CRediT author statement

Ivano Amelio, conceptualization, funding acquisition and writing (original draft, review and & editing)
Alessio Butera Writing (original draft), **Gerry Melino** Writing (review and & editing)

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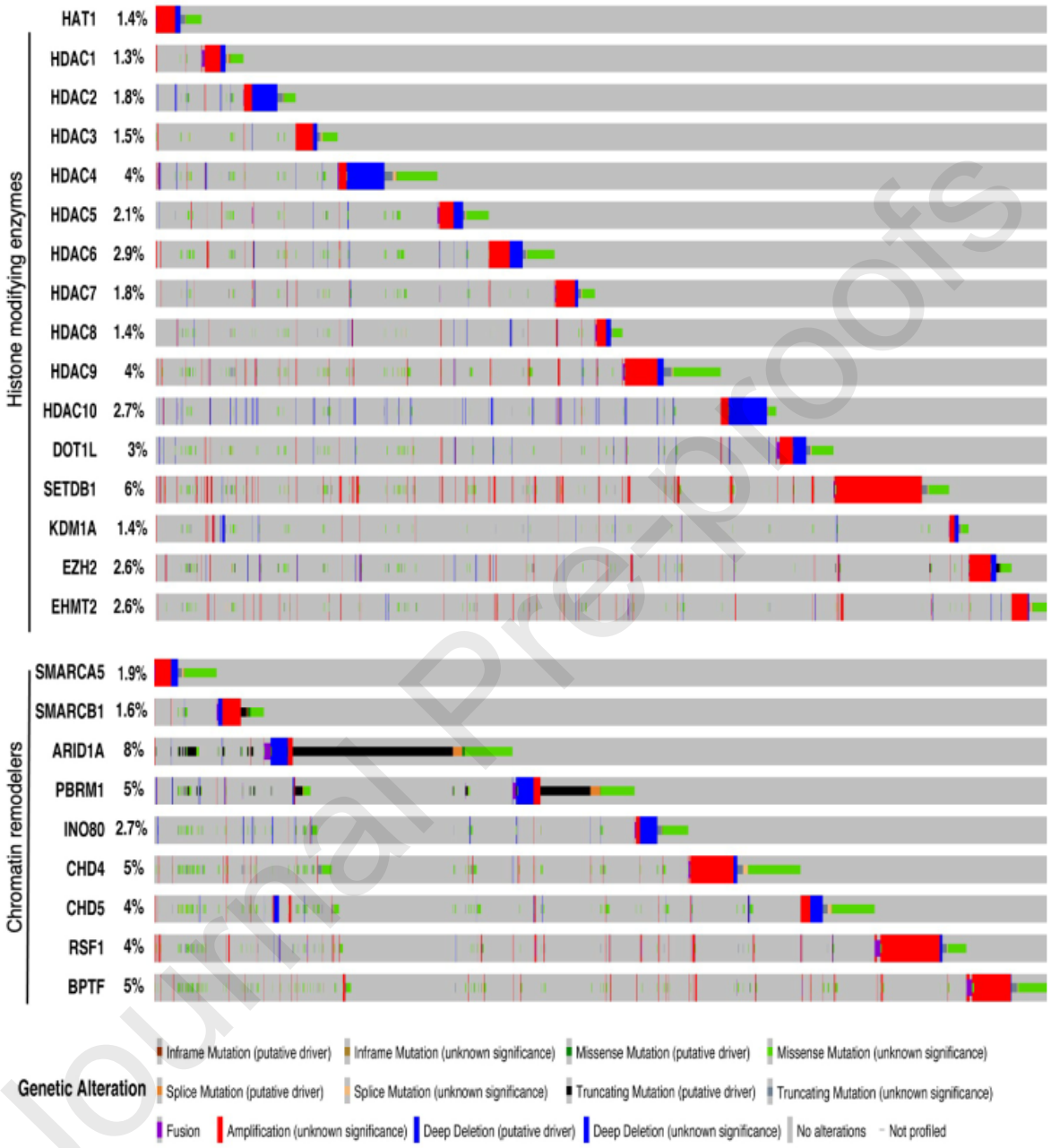
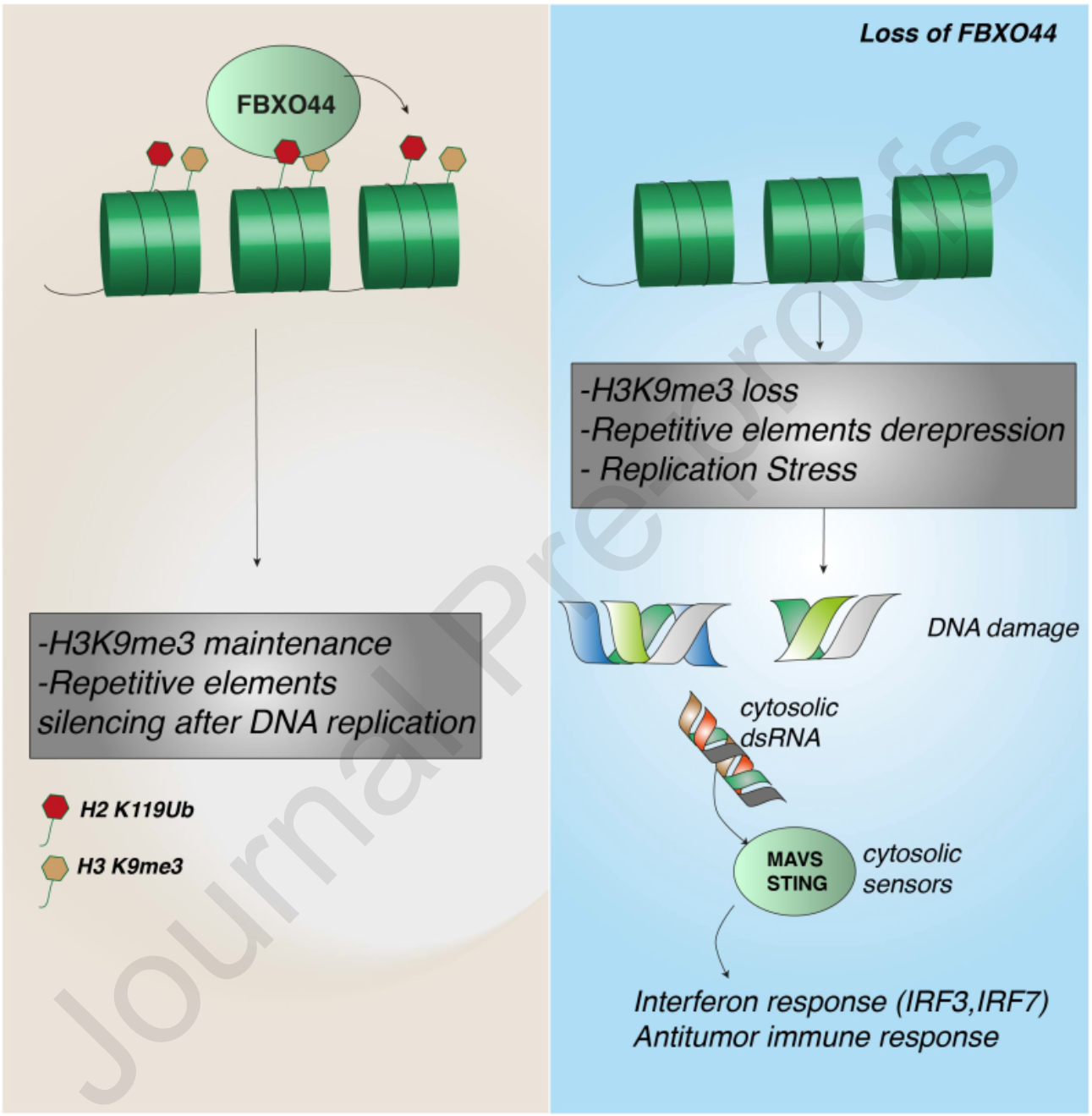


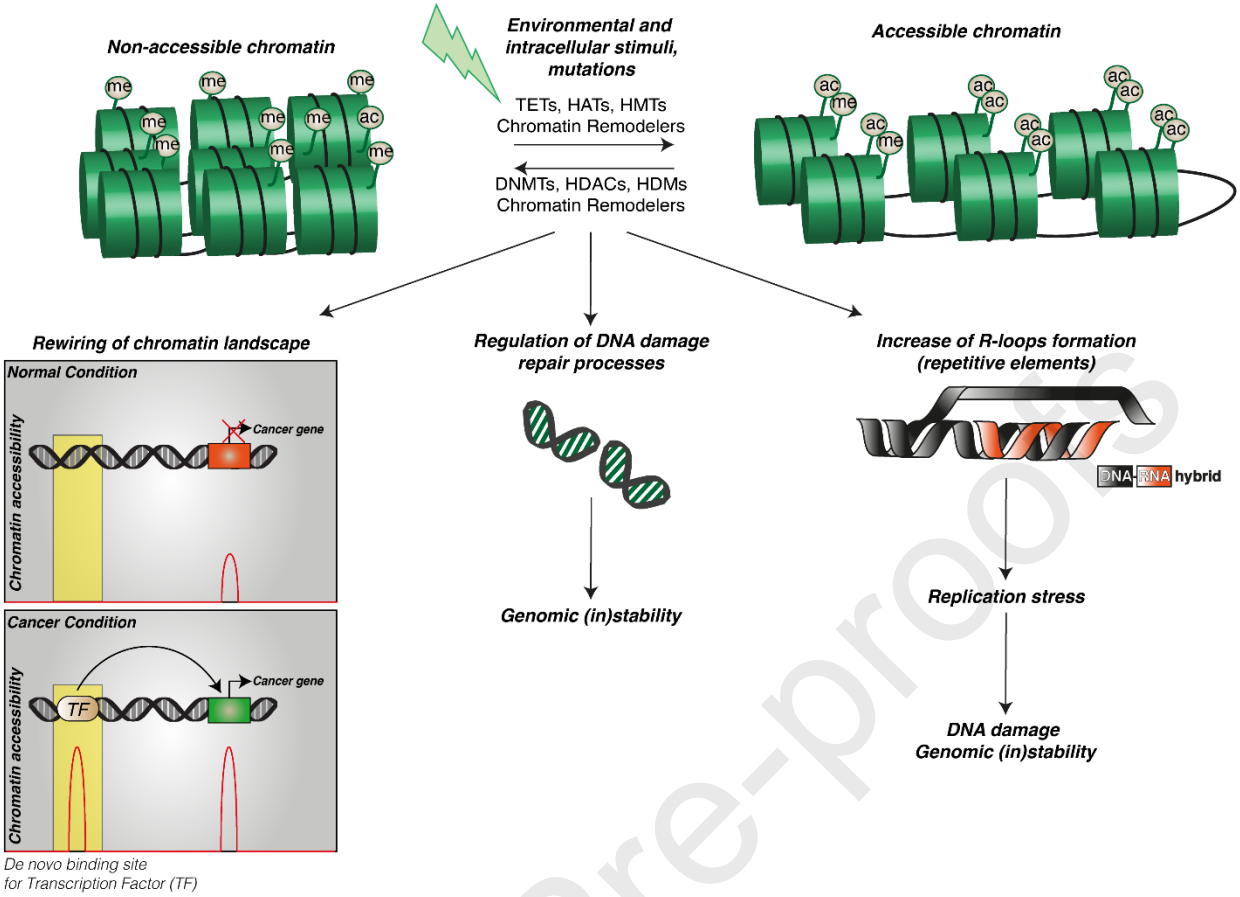


Gene	Function	Alteration	Tumor type	References
DNMT1	DNA methyltransferase	Nonsense, Missense Overexpression	Colorectal cancer Melanoma Pancreatic ductal carcinoma (PDAC)	Kanai et al.,2003 Gassenmaier et al., 2020 Gao et al., 2013
DNMT3A	DNA methyltransferase	Missense (R882H) Missense non R882 Truncating	AML AML, MDS AML, MDS	Venugopal et al., 2021; Papaemmanuil et al.,2016 Balasubramanian et al.,2018
DNMT3B	DNA methyltransferase	Overexpression	Pancreatic ductal carcinoma Colorectal cancer squamous cell carcinoma Lung carcinoma Nasopharyngeal carcinoma	Gao et al., 2013 Linhart et al., 2007; Stein et al., 2011 Chen et al., 2016 Yang et al., 2014 Wu et al., 2020
TET1	DNA demethylase	Translocation t(10;11)(q22;23 Overexpression Silencing	AML TNBC Prostate Cancer	Lorsbach et al., 2003 Good et al., 2018 Feng et al., 2015
TET2	DNA demethylase	Deletion/Silencing	Myelodysplastic syndromes, myeloproliferative disorders, AML	Delhommeau et al., 2009
TET3	DNA demethylase	Silencing Overexpression	Glioblastoma (GBM) Ovarian cancer	Carella et al., 2020 Cao et al., 2019

Table 1. Representative alterations of DNA modifying enzymes in cancer.

Gene	Function	Alteration	Tumor type	References
HAT1	Histone Acetyltransferase	Overexpression	PDAC Nasopharyngeal cancer	Fan et al., 2019 Miao et al., 2018
P300	Histone Acetyltransferase	Overexpression	Laryngeal squamous cell carcinoma	Chen et al., 2013
		Loss of expression Missense/Translocation	Leukemia, Lymphoma	Dutta et al., 2016
HDAC1-10 **SIRTs**	Histone Deacetylase	Overexpression Low Expression in rare cases	Different types of cancer	Li and Seto, 2016
DOT1L	Histone Methyltransferase (H3K79)	Overexpression Deletion or Somatic mutations	Prostate Cancer Melanoma	Vatapalli et al., 2020 Zhu et al., 2018
SETDB1	Histone methyltransferase (H3K9)	Amplification	Melanoma	Ceol et al., 2011
LSD1/KDM1A	Histone Demethylase (H3K4 and H3K9)	Overexpression	Prostate, lung, brain, breast	
		Truncating and missense mutation (germline)	Multiple Myeloma	Majello et al., 2019
EZH2	Histone methyltransferase (H3K27)	Overexpression	Prostate cancer, Breast cancer Melanoma, Bladder	Varambally et al., 2002 Xu et al., 2012 Zingg et al., 2015
		Gain of function	Non-Hodgkin's lymphoma	McCabe et al., 2015 Caganova et al., 2013
		Loss of function	MDS, T-ALL	Sashida et al., 2014 Ntziachristos et al., 2012
G9A(EHMT2)	Histone methyltransferase (H3K9)	Amplification	Breast Cancer	Wang et al., 2017
		Overexpression	Bladder cancer Colorectal cancer	Segovia et al., 2019 Chae et al., 2019

Table 2. Representative alterations of histone modifying enzymes in cancer.



De novo binding site for Transcription Factor (TF)

Epigenetic "*Drivers*" of Cancer

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Highlights

- Alterations of the cellular epigenome can "drive" cancer pathogenesis.
- Gene-environment interactions can produce gene-regulatory programs that dictate initiation and progression of cancer
- In addition to gene expression reprogramming, epigenetic deregulations can promote cancer impacting genomic integrity.
- Determination of epigenetic signature as early-stage biomarkers of disease or of therapeutic response should be a priority of future studies.