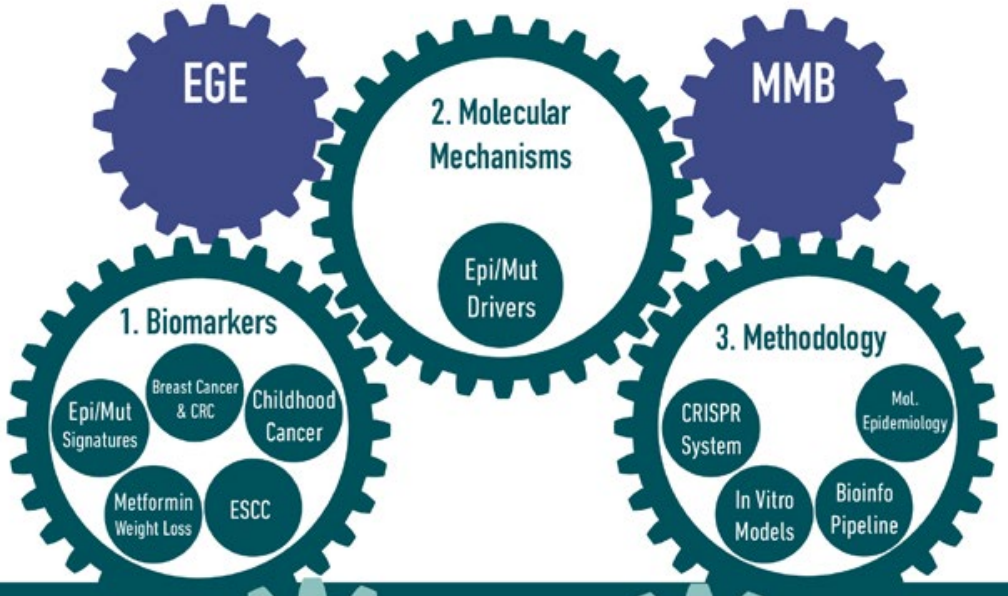
Themes & Projects

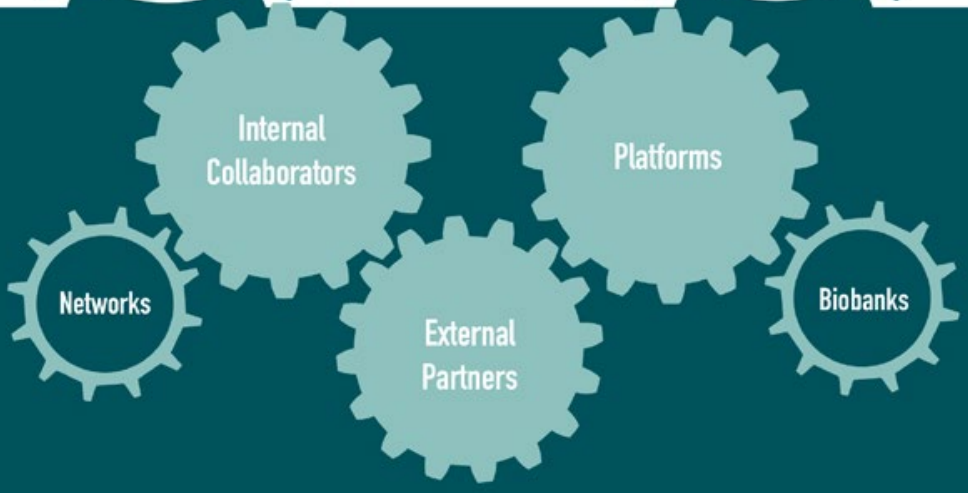
1. Identify (epi)genetic biomarkers of exposure and cancer risk to reinforce epidemiological associations

2. Investigate functional role of (epi)genetic changes and deregulated pathways induced by environmental exposures to provide biological plausibility

3. Develop (epi)genomic methodologies, profiling strategies, bioinformatics/ biostatistics tools and state-of-the-art in vitro models



Enabling Resources & Collaborators



Networks:
EpiMARK, MetBreCS, EXPOsOMICS, I4C, CLIC, EpiEARLY, PACE, CHARGE, ESCCAPE, Mutographs, PRECAMA, LYRICAN

Internal Collaborators:
BMA, ENV, GEP, GCS, ICB, IMO, NEP, NME, WCT, ITS

External Partners:
DKFZ-Heidelberg, CeMM, IGR-Paris, Univ. Oslo, Imperial College London, Duke-NUS/NCC Singapore, Univ-Minnesota, Univ-Maastricht, IEO-Milan, ISS-Rome, Mount Sinai NY, INCA-Rio, Korean Natl Cancer Institute, Sanger Inst, CRCL-Lyon, King's College London

Platforms:
NextSeq, MiSeq, Illumina BreadArray, Pyrosequencer, IP-Star Robot

Biobanks:
IARC, EPIC, I4C, DKFZ-Heidelberg, IGR-Paris, Univ-Oslo, Univ-Melbourne, Barretos, UCSD, IEO-Milan, ISS-Rome

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The main objective of the Section of Mechanisms of Carcinogenesis (MCA) is to provide the evidence base for the study of cancer causation and prevention by elucidating the molecular mechanisms by which genetic and epigenetic alterations resulting from environmental exposures and lifestyle alter critical molecular pathways and promote cancer development. The primary aims of MCA's studies are: (i) to elucidate genetic and epigenetic changes and molecular pathways induced by environmental exposures in cancer causation; (ii) to identify specific molecular changes ("signatures" of exposure) to environmental risk factors and biomarkers of cancer risk; and (iii) to develop (epi)genomic methodologies, profiling strategies, and bioinformatics tools and resources that are applicable to biobanks associated with population-based studies coordinated by IARC and external collaborators. These aims are achieved by bringing together skills in laboratory sciences, molecular epidemiology, and bioinformatics, and capitalizing on existing and developing new, multidisciplinary projects that exploit recent conceptual and technological advances as well as the uniqueness and strengths of IARC. MCA also contributes to the development of translational studies, through the discovery of mechanism-based biomarkers of exposure and cancer risk, and to cancer research that is relevant to, although not exclusive to, low- and middle-income countries. New and original research topics developed by MCA take advantage of state-of-the-art, powerful molecular and/or cell biology and functional genomics tools, recent progress in understanding of the cancer (epi) genome, and the development of genomics databases and new bioinformatics tools. These advances have facilitated the development of a multifaceted research programme aimed at identifying molecular changes associated with exposure to risk factors and providing biological plausibility for the associations that are detected in epidemiological studies. These developments have also led to synergies among several programmes at IARC and have enhanced collaborations across different Groups and/or Sections and with external researchers, creating added value for IARC's scientific activities. The Section comprises two Groups – the Epigenetics Group (EGE) and the Molecular Mechanisms and Biomarkers Group (MMB) – that work in close collaboration to create synergies and better exploit and further expand unique research tools and expertise.

Epigenetics Group (EGE)

The overarching aim of the Epigenetics Group (EGE) is to advance the understanding of the role of epigenetic changes and pathways induced by environmental factors in cancer causation, underpinning studies of etiology, carcinogen evaluation, and prevention. EGE exploits new concepts in cancer epigenetics, the availability of unique population-based cohorts, and recent technological advances in epigenomics (Van Baak et al., 2018; Woo et al., 2018; Josipović et al., 2019; Küpers et al., 2019; Patil et al., 2019). EGE also develops epigenomic methodologies, profiling strategies, and bioinformatics tools applicable to population-based cohorts and molecular epidemiology studies coordinated by IARC researchers and external collaborators (Felix et al., 2018; Herceg et al., 2018; Alcala et al., 2019).

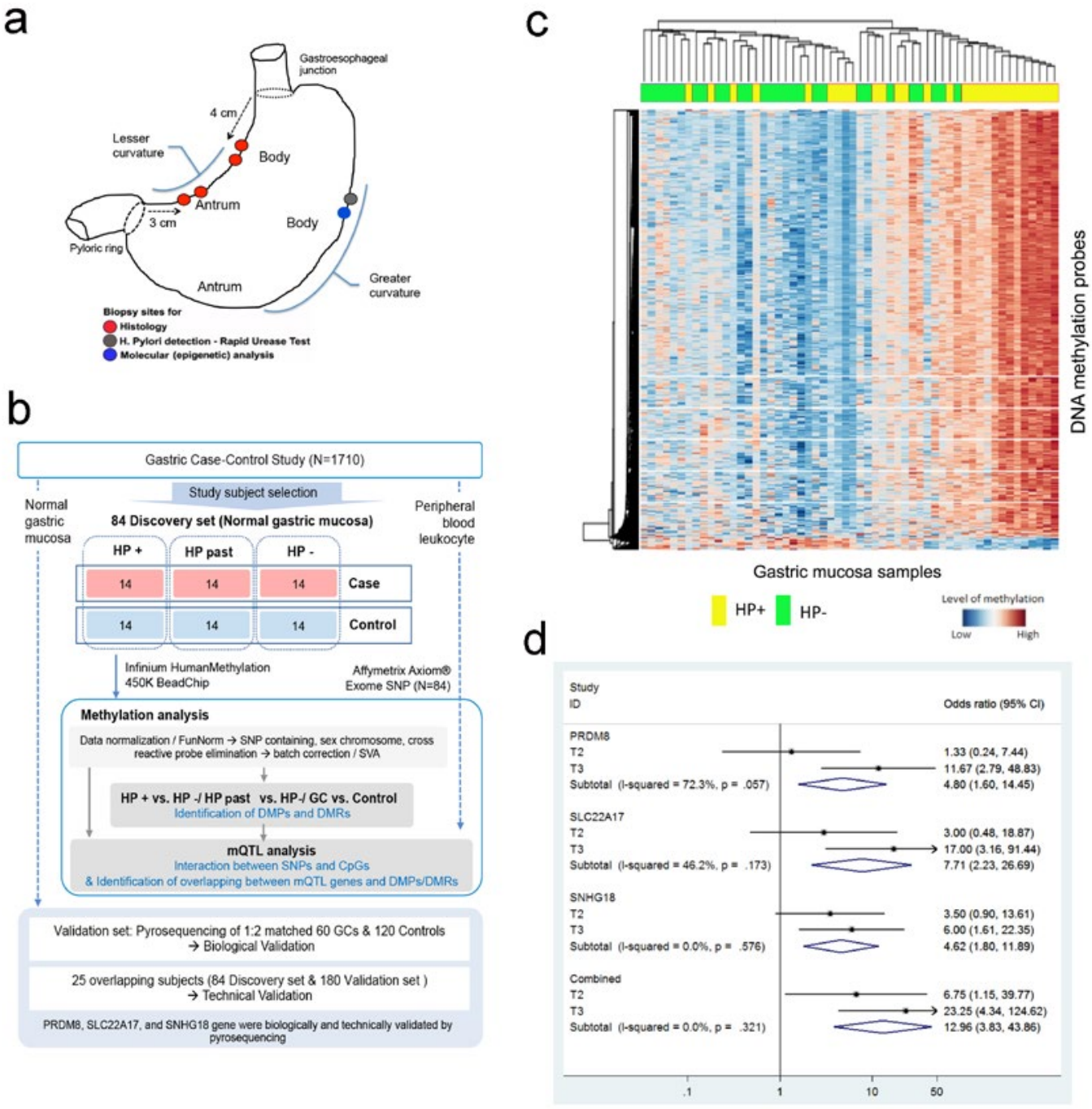
Genome-wide profiling of normal gastric mucosa to identify *Helicobacter pylori*-associated epigenetic changes associated with cancer risk

Infection with the bacterium *Helicobacter pylori* is thought to be the single most common cause of gastric cancer, which is the third most common cause of cancer-related deaths worldwide. EGE investigated the impact of both current *H. pylori* infection and epigenetic memory of past (eradicated) infection on aberrant epigenetic (DNA methylation) patterns. In collaboration with the National Cancer Center of the Republic of Korea, EGE analysed a series of normal gastric mucosa from cases and controls representing various *H. pylori* and gastric cancer statuses using genome- and epigenome-wide approaches (Woo et al., 2018). A total of 438 differentially methylated regions (DMRs) were associated with *H. pylori* infection, most of which showed marked reversibility, albeit selective stability of specific DMRs ("epigenetic memory"), after *H. pylori* clearance. Interestingly, 152 DMRs were associated with cancer risk independent of *H. pylori* status in normal gastric mucosa (Figure 1). The comprehensively characterized methylome changes associated with *H. pylori* infection and gastric cancer risk in this study may serve as potential biomarkers for early cancer progression in tumour-free gastric mucosa.

Pan-cancer genome and transcriptome analysis and orthogonal experimental assessment of epigenetic driver genes and their link to environmental carcinogens

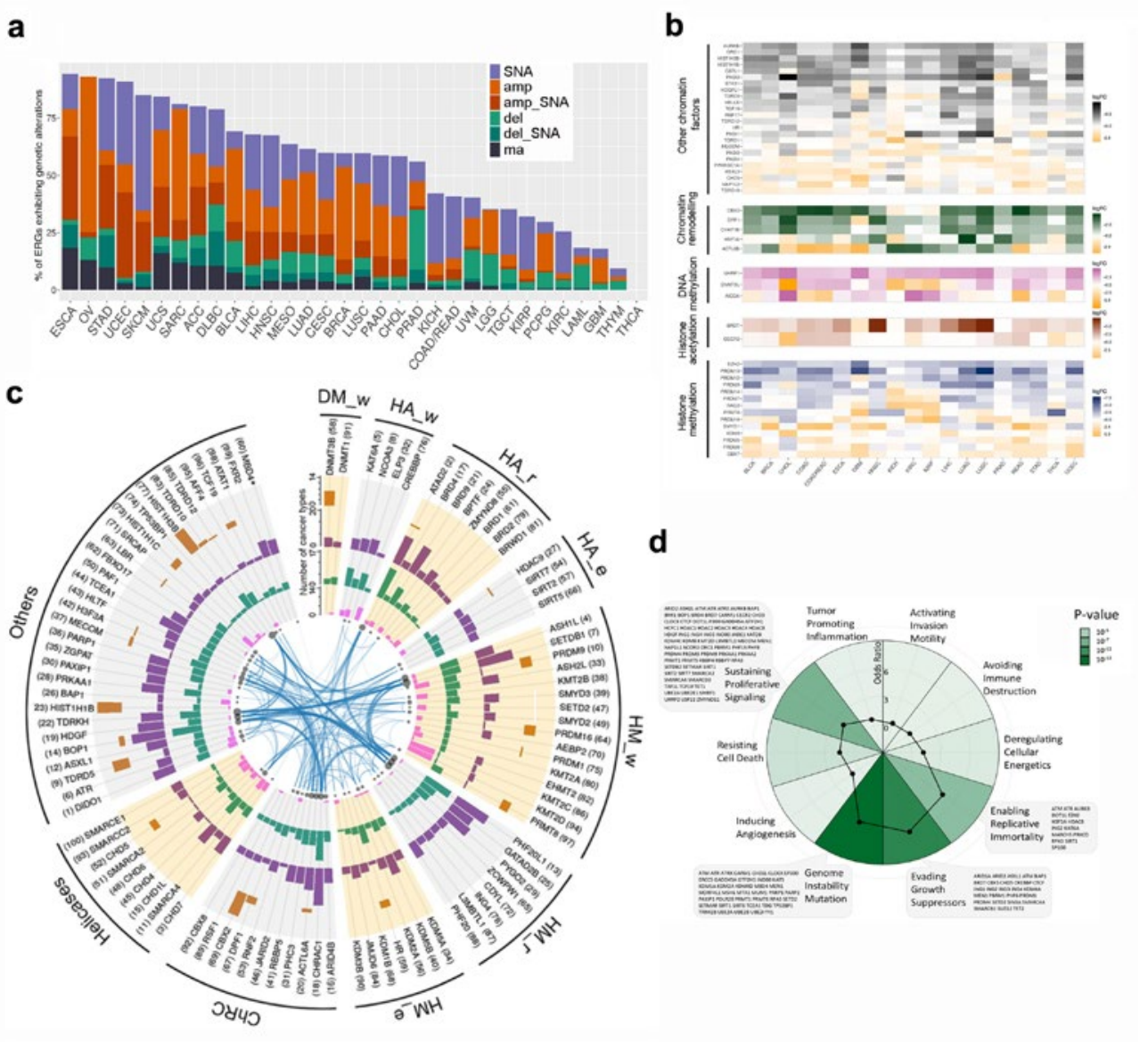
The recent discovery of numerous genetic alterations in the genes that directly regulate the epigenome (referred to here as epigenetic regulator genes [ERGs]) in human cancers sparked a debate on whether these genes potentially act as drivers of tumorigenesis and on the mechanisms that fuel epigenome changes that are rampant in human malignancies. EGE developed and tested a conceptual framework for experimental identification and functional characterization of the mechanistically important epidrivers that reshape the epigenome and contribute to cancer phenotypes (see text box). First, the Group conducted a pan-cancer and integrative analysis of global genetics- and transcriptome-based disruption of a curated list of 426 ERGs in 33 cancer types on the basis of sequencing information from 10 845 tumour samples and 730 normal tissues (see text box). A high rate of alterations in ERGs was

Figure 1. DNA methylome profiling of normal gastric mucosa by *Helicobacter pylori* infection status. (a) Gastric mucosa biopsy samples for molecular (epigenetic) analysis were obtained from the greater curvature of the gastric body (blue circle). (b) Flow chart illustrating the overall design of the study. Subjects were stratified by *H. pylori* infection status (current [HP+], negative [HP−], or past [HP past]) and cancer status (case or control), and were matched for age, sex, and Laurén classification (for cases). (c) Cluster heat map analysis of differentially methylated positions (DMPs) with delta β ≥ 20%. The rows represent probes for the 1924 DMPs, and the columns represent individual HP+ and HP− samples. The cells are coloured according to the level of methylation. Among these DMPs, 52 CpG sites (2.7%) were hypomethylated and 1872 (97.3%) were hypermethylated. (d) Putative biomarker genes for gastric cancer incidence and their combined methylation score. Odds ratios and 95% confidence intervals (CIs) of gastric cancer by tertile (T) of methylation levels for three putative biomarker genes. DMR, differentially methylated region; mQTL, methylation quantitative trait loci; SNP, single-nucleotide polymorphism. Figure adapted from Woo et al. (2018). © 2018 IARC/WHO; licensed by UICC.



identified for most cancer types, with recurrent pan-cancer mutations and copy number alterations (CNAs) in specific ERGs or classes of ERGs, which were tightly linked to changes in gene expression (Figure 2). Further, EGE applied a novel bioinformatics approach (Pan-Cancer Driver) that integrates the strengths of various driver prediction algorithms and accounts for multiple –omics layers, to reveal ERGs with driver potential in cancer (Figure 2). Finally, the

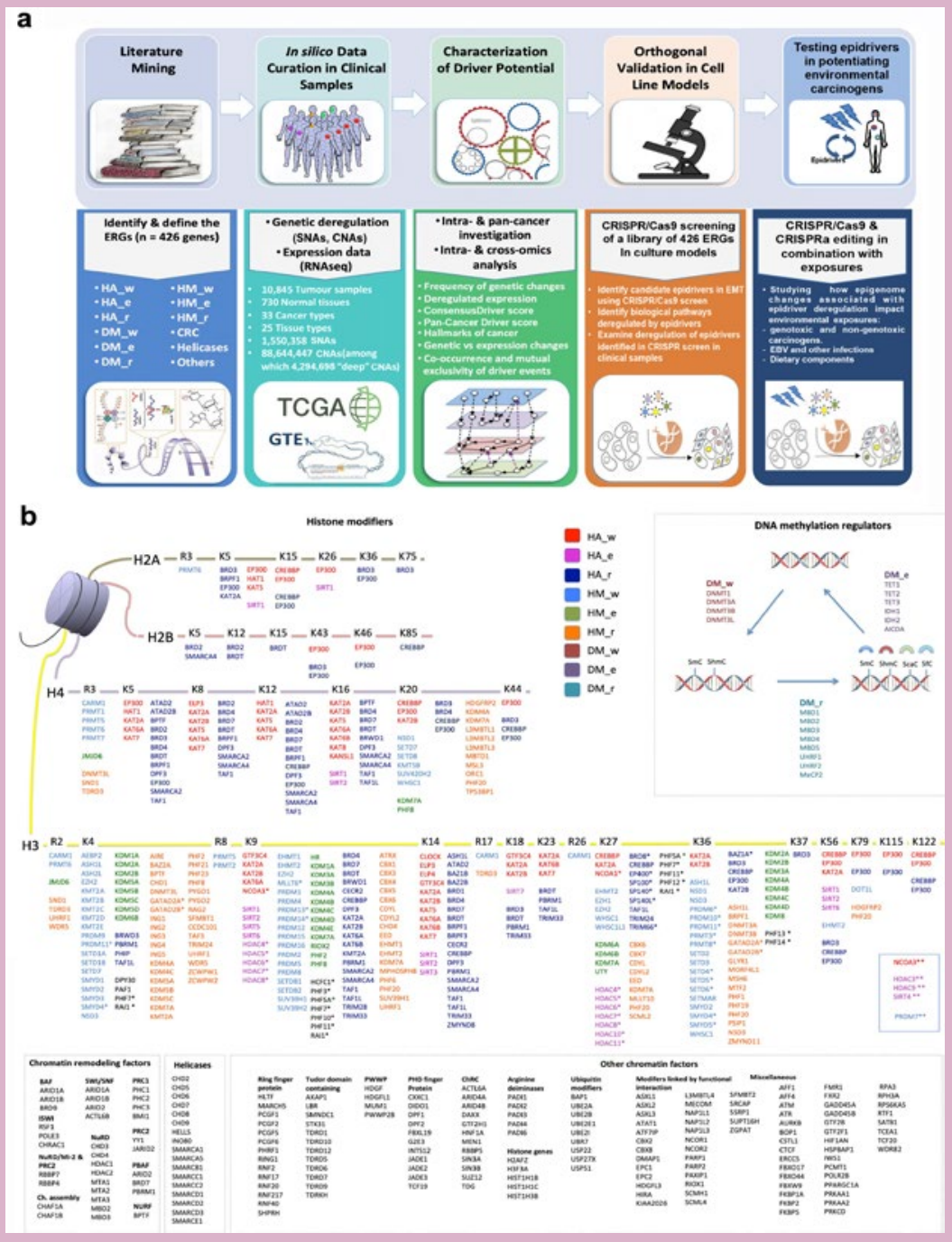
Figure 2. Pan-cancer genome discovery of epigenetic driver genes. (a) Pan-cancer analysis of genetic alterations across epigenetic regulator gene (ERG) categories and classes. The bar plot shows the percentage of ERGs exhibiting different types of genetic deregulation by cancer type. Genetic alterations: single-nucleotide alteration (SNA), deep copy number amplification (amp), deep amplification co-occurring with SNA (amp_SNA), deep copy number deletion (del), deep deletion co-occurring with SNA (del_SNA), and multiple alterations (ma). ERGs are considered altered (deep amplification, deep deletion, or SNA) if at least 1% of samples harbour these alterations. (b) The heat maps show the most differentially expressed ERGs comparing tumour samples with adjacent normal tissues among cancer types. Only the top differently expressed ERGs with |log fold change (FC)| > 3 and false discovery rate (FDR) < 0.05 are annotated. (c) Characterization of the driver potential of ERGs. Top 100 ERGs by pan-cancer driver score using SNA (5% of samples), copy number alteration (CNA) (5% of samples), and expression data (15% of samples with significant z-score or FDR < 0.05 with $\log_2$ FC > 1). Results are presented as bar plots counting the number of cancers in which a given gene has a particular genomic or expression alteration. From inner to outer track: pink, SNAs; green, CNAs; purple, z-score; orange, log2 FC. Genes are aggregated by their functional features. (d) The spider pie chart shows enrichment of the 426 ERGs in pathways affecting the 10 hallmarks of cancer; the corresponding *P* values are illustrated by green gradients and the odds ratios by black spots. The names of ERGs overlapping with the four significantly enriched hallmarks are indicated. Figure based on EGE work (unpublished). © IARC.



Group developed and applied epigenome-wide functional screens (based on the CRISPR/Cas9 system) targeting all 426 ERGs in vitro and identified candidate ERGs with a driver role conferring on cancer cells the traits associated with the hallmarks of cancer. This is the largest and most comprehensive analysis to date of the cancer-associated disruption of ERGs and is the first experimental effort to specifically identify epidrivers in oncogenic processes, providing crucial insights into the deregulation of ERGs and their functional impact in cancer (Halaburkova et al., 2019). Current and future studies (in collaboration with MMB and external partners) are aimed at examining how epidriver events synergize with environmental carcinogens in cancer causation.

Strategy for identifying and characterizing epigenetic driver genes and their environmental determinants

General pan-cancer genomic and experimental strategy for identifying and characterizing epigenetic driver genes and their environmental determinants. (a) A five-stage approach adopted to identify and assess epigenetic regulator genes (ERGs) with driver potential includes: (1) comprehensive literature mining, (2) in silico data curation in clinical samples, (3) modelling the driver potential of candidate genes, (4) CRISPR/Cas9 screen for orthogonal in vitro assessment of driver potential, and (5) characterizing the synergy between epidrivers and environmental exposures. (b) A compendium of ERGs included in the study, comprising 426 ERGs categorized as histone modifiers, chromatin remodellers, or DNA methylation regulators. Histone acetylation, histone methylation, and DNA methylation modifiers are further stratified as "writers" (w), "editors" (e), or "readers" (r). The remaining ERGs are categorized as chromatin remodelling factors (ChRC), helicases, or other chromatin modifiers (some of which are further divided into subgroups on the basis of function or their presence in molecular complexes). An asterisk (*) denotes the histone-modifying genes whose functions are not well characterized and which are therefore assigned based on Encyclopedia of DNA Elements (ENCODE) chromatin immunoprecipitation (ChIP) sequencing data; two asterisks (**) denote the histone-modifying genes without assignment of residues in the histone tails. CNA, copy number alteration; EBV, Epstein–Barr virus; EMT, epithelial-to-mesenchymal transition; GTEx, Genotype-Tissue Expression database; SNA, single-nucleotide alteration; TCGA, The Cancer Genome Atlas.



Epigenetic regulation of the mitochondrial genome in cancer

In a recent study, EGE examined epigenetic modification in the genome of mitochondria, the powerhouses of cells, and revealed the first reported evidence of DNA methylation patterns of the mitochondrial genome at high resolution. Notable differences were seen between the methylation patterns in normal cells and in cancer cells (Figure 3). The study examines the technical considerations that have so far impeded the study of mitochondrial epigenetics, and addresses the potential functional consequences of methylation of mitochondrial DNA in cancer (Patil et al., 2019). Cancer cells have a greater need for energy compared with normal cells, and mitochondrial dysfunction plays an important role in tumorigenesis. These findings could lead to new methods of identifying novel cancer biomarkers or targeting the energy metabolism of cancer cells.

Identifying epigenetic changes induced by in utero and adult-life exposures and their causal relationship with cancer

EGE leads a multidisciplinary study investigating the causal relationship between in utero and later-life exposures and an increased risk of cancer in childhood and adulthood. Building on a unique epigenetic epidemiology framework at IARC and several major international consortia, the Group has made major advances in identifying epigenetic signatures of in utero (Alfano et al., 2018; Gruzieva et al., 2019; Küpers et al., 2019) and later-life (Woo et al., 2018; Johansson et al., 2019a; Perrier et al., 2019) exposures and in deciphering their effects on phenotypic outcomes, with a primary focus on childhood cancer and selected adult cancer types (Table 1).

Figure 3. Mapping epigenetic modifications of the mitochondrial genome in normal and cancer cells. Schematic representation of (a) mitochondrion and (b) mitochondrial genome. (c) Baseline patterns of the mitochondrial DNA (mtDNA) methylation methylome in normal and cancer breast cells sequenced on the next-generation sequencing platform using the protocol established by EGE. The circular plot represents genomic position (1–16 kb) of all methylated cytosines with respect to sequence order. Each segment of the circle represents a separate functionally relevant region, transfer RNA (tRNA), ribosomal RNA (rRNA), gene, or displacement loop (D-loop). The *y*-axis indicating methylation level is represented on the left side of the D-loop segment. The large outer ring displays methylation at each cytosine within the heavy strand (H-strand), whereas the large inner ring displays methylation at each cytosine on the light strand (L-strand). Thin inner bands indicate the genomic position of all cytosines within the H-strand or L-strand sequence. Note that global mtDNA methylation patterns differ between cancer and normal cells. (d) Summary statistics of the frequency of mitochondrial mCpN context in liver cells. (e) Methylation index (MI) across tRNA-encoding regions in breast cancer versus normal cells. Each horizontal segment compares the MI within tRNAs that have been grouped according to the amino acid they carry (acidic, basic, aromatic, or hydrophobic). The left panel indicates MI across the H-strand, and the right panel indicates MI across the L-strand. (f) Comparative box plot indicating significant ($P < 0.001$) difference of mean methylation across gene-encoding regions of normal versus cancer cells in each strand. (g) Density plot of the distribution of methylation values along the D-loop region. Figure adapted from Patil et al. (2019). © Patil V, Cuenin C, by permission of Oxford University Press.

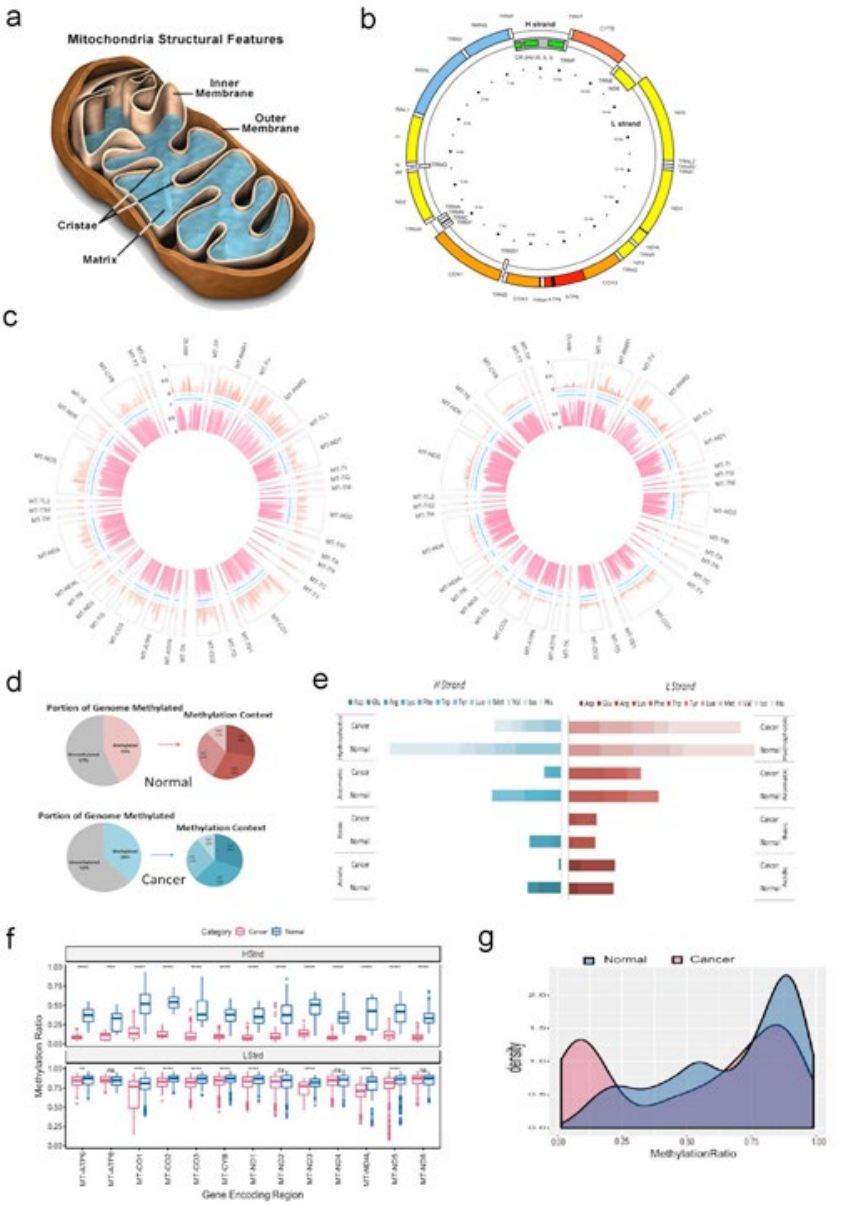


Table 1. Summary of epigenetic signatures of exposures, phenotypes, and cancer risk identified to date

Exposure/cancer risk	Study (sample size)	Number of significant CpGs[a]	Major finding	Reference
Exposures during pregnancy				
Paternal pre-pregnancy BMI	9340 (19 cohorts)	0 [0]	Little evidence of association was seen between paternal pre-pregnancy BMI and offspring methylation, including at imprinted regions	In preparation
Gestational diabetes	3677 (7 cohorts)	3 [2]	Little evidence of association was seen between gestational diabetes and offspring methylation	Submitted
Season of conception or birth	120 (1 cohort); expansion into other cohorts is in under way	Only DMRs reported	Dry vs rainy season in rural Gambia (hence maternal nutrition) altered the methylation of the tumour suppressor metastable epiallele, *VTRNA2–1*, and exhibited the hallmarks of metabolic imprinting	In progress
Socioeconomic status	914 (1 cohort); expansion into other cohorts is in under way	4 [1]	Among four major socioeconomic indicators (maternal and paternal education and occupation), only maternal education was associated with methylation levels at birth	Alfano et al. (2019); in progress
Maternal infection	In progress	In progress	NA	In progress
Intermediate phenotypes				
Birth weight	8825 (24 cohorts)	8170 [914]	Birth weight was largely associated with epigenomic variations in newborns, with a difference in birth weight ranging from −183 g to 178 g per 10% increase in methylation. Ten CpGs remained nominally associated with birth weight later in childhood (age 2–13 years), adolescence (age 16–18 years), and adulthood (age 30–45 years).	Küpers et al. (2019)
Gestational age	3648 (17 cohorts)	NR [8899]	Gestational age was largely associated with the newborn's epigenome. For most CpGs, the effect of gestational age on methylation diminished over time and stabilized after school age.	Submitted
Early-life end-points				
Childhood leukaemia/ CNS tumours	In progress	In progress	In progress	In progress
Adult or life-course exposure				
Alcohol/folate	EPIC cohort	24 DMRs (folate), 90 DMRs (alcohol)	Weak association with DMPs, but the DMR analysis revealed a total of 24 and 90 regions associated with dietary folate and alcohol, respectively	Perrier et al. (2019)
Estrogen (lifetime exposure)	EPIC-Italy (*n* = 216)	694 CpG sites	The EWAS identified 694 CpG sites associated with an estimated lifetime estrogen exposure model; in vitro follow-up study	Johansson et al. (2019a)
Oral contraceptive use	EPIC cohort	Large number of DMPs	Strong association with DMPs; replication using an independent cohort in progress	In preparation
Helicobacter pylori	National Cancer Center of the Republic of Korea study	1924 DMPs and 438 DMRs	1924 DMPs and 438 DMRs were found to be associated with *H. pylori* infection, most of which were hypermethylated	Woo et al. (2018)
Cancer risk				
Breast cancer risk	Meta-analysis, 4 cohorts (1663 cases and 1885 controls)	None	Methylation measured at individual CpGs (using 450K arrays) was not associated with risk of breast cancer	Bodelon et al. (2019)

BMI, body mass index; CNS, central nervous system; DMP, differentially methylated position; DMR, differentially methylated region; EPIC, European Prospective Investigation into Cancer and Nutrition; EWAS, epigenome-wide association study; FDR, false discovery rate; NA, not applicable; NR, not reported; vs, versus.
[a] Number of statistically significant CpGs (FDR < 0.05) identified. The number of Bonferroni-significant CpGs is shown in square brackets.

Molecular Mechanisms and Biomarkers Group (MMB)

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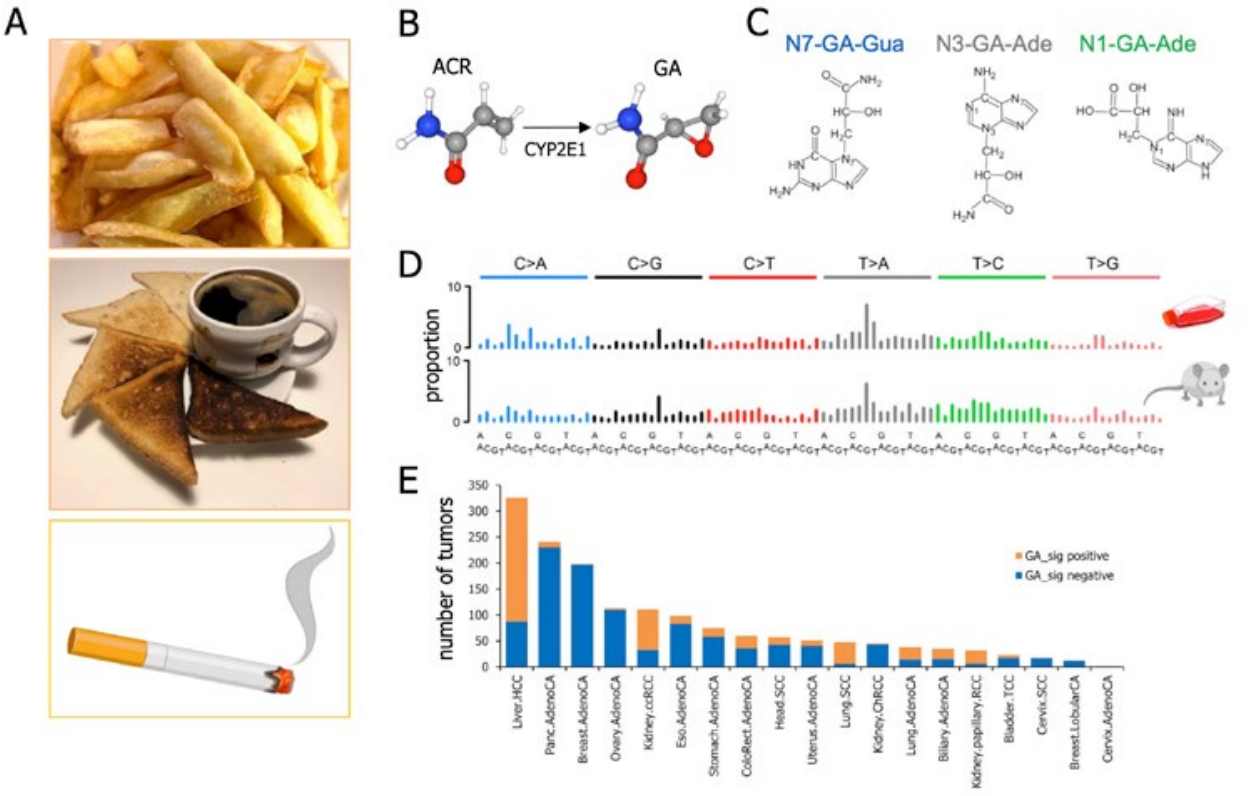
The overarching goal of the Molecular Mechanisms and Biomarkers Group (MMB) is to develop and coordinate international collaborations aiming to determine molecular processes and markers of carcinogenesis associated with specific environmental, iatrogenic, and lifestyle risk agents. The impact of cancer risk agents on the genome is studied in experimental systems and in human and animal tissues. Furthermore, MMB devises experimental and bioinformatic methods (Marques et al., 2019) applicable to experimental and molecular cancer epidemiological studies. Taken together, the activities of MMB support cancer prevention strategies, including evidence-based carcinogen evaluation and classification (Samet et al., 2019).

Mutational signature of glycidamide (a metabolite of acrylamide) is widespread in human cancers

Acrylamide is carcinogenic in rodents and is classified by the IARC Monographs programme as probably carcinogenic to humans (Group 2A). It is present in common foods processed at a high temperature, for example, potato chips, French fries, crackers, bread, cookies, breakfast cereals, coffee, canned black olives, and prune juice. Tobacco smoke is another major source of acrylamide exposure in humans. To date, epidemiological studies have yielded rather inconclusive evidence as to the association between exposure to acrylamide and cancer, except for weak positive trends for cancers of the kidney, endometrium, and ovary in never-smokers. The mutagenicity of acrylamide is attributed to glycidamide, its reactive metabolite. By using genome-wide DNA sequencing of cell clones and of mouse lung tumours arising from glycidamide exposure, MMB identified a novel mutational signature of glycidamide. The signature is remarkably stable across the experimental models (Figure 4), and its composition corresponds to known pre-mutagenic DNA adducts. Using innovative targeted computational screens and mutation spectra modelling in synthetic genomes, the glycidamide

Figure 4. The mutational signature of glycidamide, a metabolite of acrylamide, is widespread in human cancers. (A) Some common sources of human exposure to acrylamide. (B) Metabolic activation of acrylamide (ACR) to a reactive epoxide glycidamide (GA) by CYP2E1 enzymatic activity (source: PubChem). (C) Major DNA adduct species identified in mouse tissues and cells upon exposure to ACR or GA. (D) The mutational signature of GA observed in vitro (upper panel) and in vivo (lower panel). (E) Total tumour counts versus human tumour types (total, 19) characterized by subsets harbouring the mutational signature of GA (labelled in orange). © IARC.



signature was identified in 34% of 1584 tumour genomes from the Pan-Cancer Analysis of Whole Genomes (PCAWG) of the International Cancer Genome Consortium. The tumours positive for the glycidamide signature comprised 19 human tumour types from 14 anatomical organs, and the signature was most enriched in cancers of the lung, kidney, liver, bile duct, head and neck, stomach, uterus, and oesophagus, and was present to a lesser extent in other cancer sites. These results (Zhivagui et al., 2019) reveal an unexpectedly widespread contribution of acrylamide-associated mutagenesis to human cancers. Acrylamide and glycidamide have recently been assigned a high priority for evaluation by the IARC Monographs Priorities Group (Marques et al., 2019), and new molecular cancer epidemiology studies are addressing the potential causal effects of acrylamide in human carcinogenesis.

Toxicity and genomic DNA damage by cobalt metal and cobalt salt

Various occupational, environmental, and clinical settings can lead to human exposure to cobalt and cobalt compounds, which are known to be carcinogenic in rodents and are possibly carcinogenic to humans (IARC Group 2B). Despite some evidence for in vivo and in vitro toxicity, the exact mechanisms underlying cobalt-associated tissue and DNA damage are not well understood. MMB aims to determine the damaging effects of cobalt on DNA by conducting integrated toxicogenomic analyses in exposed human lung cell lines propagated in two-dimensional cultures or under three-dimensional air–liquid interface conditions, in mouse primary fibroblasts, and in mouse lung tumours arising from chronic treatment with cobalt (Figure 5A). Treatment-specific genotoxic and oxidative damage effects were observed across the model systems. Furthermore, whole-genome sequencing of cell clones and mouse lung tumours yielded mutation spectra specific to cobalt exposure, indicating a genome-wide mutational signature of oxidative DNA damage; this observation was then validated by biochemical analysis (Figure 5B, C). These results provide a basis for future molecular epidemiology studies exploring the link between cobalt exposure and human cancers, further justified because cobalt and cobalt compounds have been assigned a high priority for evaluation by the IARC Monographs Priorities Group (Marques et al., 2019).

The EVAMOVAIRE2 project, conducted in collaboration with Centre Léon Bérard and the Lyon Sud Hospital Center, aims to elucidate the patterns of genomic damage in ovarian tumours as a result of exposure to asbestos. The INVITROMICS project, conducted in collaboration with EGE, aims to identify novel molecular markers of early tumorigenesis in experimental models of cell transformation. The OROQAT project, conducted in collaboration with the Section of Environment and Radiation, aims to investigate the cancer driver mutations in oral and oropharyngeal cancers of qat users from Ethiopia, to define markers of qat-chewing-specific mutagenesis and carcinogenesis. In the PUVARCC project, the genome-wide effects of 8-methoxypsoralen, a component of the treatment of skin diseases by psoralens and ultraviolet radiation class A (PUVA therapy), are being investigated for potential contributions to the development of renal cancer.

Figure 5. Toxicity and genomic DNA damage induced by cobalt metal and cobalt salt. (A) The study design integrating two-dimensional (2-D) and three-dimensional (3-D) mouse and human cell culture exposure systems (mouse lung tumours induced by chronic inhalation of cobalt metal particulate aerosol) (source: United States National Toxicology Program) and mining of public pan-cancer genome data. (B) The main mutational signatures identified in cells and mice; top panel: the accumulation of C > A mutations suggests oxidative-stress-related damage of guanines. (C) Significantly increased levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) identified in mouse fibroblast cells treated with cobalt metal and cobalt salt, 24 hours after exposure. ALI, air–liquid interface; Co, cobalt; DB, database; FFPE, formalin-fixed, paraffin-embedded tissue; ICGC, International Cancer Genome Consortium; MEF, mouse embryonic fibroblast; PCAWG, Pan-Cancer Analysis of Whole Genomes. © IARC.