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Thesis: Genetic, molecular and environmental factors involved in the risk of colorectal malignancies, their prognosis and therapy response

Extended summary to the DSc. Thesis

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CONTENT

1. Introduction, carcinogens and carcinogenesis.

The disruption of genomic integrity due to the accumulation of various kinds of DNA damage, altered DNA repair capacity, and changes in telomere homeostasis represent important prerequisites for malignant transformation. By adopting this hypothesis, we assumed that arising accumulation of DNA damage, subsequent mutations, alterations in telomere homeostasis and genomic instability is a continuum of pleomorphic processes contributing to both intra- and inter-tumor heterogeneity. Our long-lasting effort has therefore been dedicated to the links between DNA damage, DNA repair, and telomere homeostasis, particularly in relation to the cancer onset, progression and therapy outcome. In this context, DNA damage response (DDR) represents a signalling network to process DNA damage by activating network comprising cell cycle checkpoint induction, DNA repair, and induction of cell death. The board of experts at International Agency for Research on Cancer (IARC) coined the term 'carcinogenic risk' for assessment, whether the particular agents (or defined mixture) are capable of causing cancer.

In our studies we have shown that DNA damage induced by alkylating agents occurs mainly at various positions of purines. The biological consequences are related to the localization of the damage (breakage of glycosidic or phosphodiester bonds, the latter resulting in strand breakage, Dimroth rearrangement or hydrolytic deamination). Improper function of polymerases during DNA replication (base substitution mismatches, insertion-deletion mismatches) or physiological metabolic processes in the body represent endogenous source of DNA damage [1,2]. The purine moieties of nucleic acids pose important targets for hydroxyl radicals, a consequence of a misbalance between oxidant and antioxidant molecules. Enhanced oxidative DNA damage occurs during increased lipid peroxidation and inflammation; if unrepaired it is mutagenic and contributes to genomic instability [3,4]. Double-strand breaks (DSBs) are associated with ionizing radiation, intra- or inter-strand crosslinks by UV radiation [5]. A complex biological process of DNA repair ensures genomic stability and integrity of the cells via several distinct pathways that remove different types of DNA damage [6]. All DNA repair pathways are encoded with more than 150 human DNA repair genes [7].

2. Tracking the effects of industrial/environmental chemicals

Three decades ago we have dedicated our activity towards high-volume industrial chemicals acrylates and metacrylates that require metabolic activation. We have addressed metabolism, disposition, reaction with glutathione and DNA of these compounds, classified by IARC as possible human carcinogens (see publications [8–13]). We have also investigated genotoxic, cytotoxic and clastogenic effects of heavy metals (such as Chromium^{vi}) [14,15]. The author has also participated as an expert in re-evaluation of carcinogenicity of quinoline, styrene and styrene-7,8-oxide by IARC in 2018 [16]. The summary has appeared in Lancet Oncol. 2018.

2.1. DNA damage and its determination.

Unrepaired DNA damage and subsequent DDR disruption underlie the genomic instability and accompany tumorigenesis and cancer progression [17]. Understanding of these processes is inevitable in comprehension of malignant transformation.

2.1.1. DNA damage and its determination-*in vitro* studies.

Many xenobiotics exhibit the affinity to lipidic structure and they need to undergo metabolic conversion to make them excretable. This process produces highly reactive epoxides that attack biological macromolecules and DNA (DNA adducts). In this context, we have investigated absorption, distribution, elimination and haemoglobin and DNA adduct formation in the rats after inhalation of individual C2-C8 1-alkenes. All 1-alkenes caused haemoglobin and DNA adducts, although the levels of adducts in haemoglobin and DNA decreased with increasing number of carbon atoms in the chain [18]. Similarly, N-7 guanine platination and methylation have been studied as well [19]. A sensitive ^{32}P-postlabelling technique coupled with HPLC has been optimized for the detection of various DNA adducts in order to achieve high reproducibility in separating complex mixtures of DNA adducts [20]. The same technique has been optimized for the DNA adducts derived from 12 polycyclic aromatic hydrocarbons after metabolic activation [21]. Most of our studies on DNA adducts investigated styrene and its principal metabolite, styrene-7,8-oxide (SO); such as the reactivity of SO with nucleic acid constituents, the properties of resulting DNA adducts and their stabilities (imidazole ring-opening and depurination) [22–24]. Stability of phosphodiester bonds and

subsequent strand breakage have been addressed in another manuscript [25]. The reaction kinetics and modifications of particular positions at purines and pyrimidines, including their stabilities, are shown in [2,26–29]. The stabilities of SO-DNA adducts and their quantitation are critical prerequisite for the high specific and sensitive methods for human biomonitoring [30,31]. Similarly, formation and stability of dimethyl sulphate, ethylene oxide and malonaldehyde adducts at deoxyguanosine 3´-monophosphate are reported in [32,33]. DNA damage (or DNA adducts), unless repaired, results in various mutations, mainly base substitutions (transitions or transversions). This miscoding potential of individual adducted bases has been intensely studied [34–36] and DNA adducts in *in vitro* study were investigated in association with HPRT mutant frequencies and DNA strand breaks (SSBs) [37]. The biological relevance of most abundant N7 DNA adducts has further been studied *in vitro* for the development of the very sensitive qualitative and quantitative method for their ultimate determination in humans [38,39]. The modified 32P-postlabelling method was applied for the detection of N-7-(2-hydroxy-phenylethyl) guanine adducts in DNA and human embryonal lung cells treated *in vitro* with SO. We observed interesting associations between DNA adduct formation and removal over time in parallel with appearance and disappearance of SSBs [40]. We have recently demonstrated that Ganoderma lucidum induces oxidative DNA damage selectively in colorectal cancer (CRC) cell lines, whereas it protected non-malignant cells from the accumulation of reactive oxygen species. Accumulation of DNA damage caused sensitization of cancer cells to 5-Fluorouracil (5-FU) improving its anticancer effect. The results were replicated in *in vivo* study: Ganoderma lucidum co-treatment with 5-FU increased the survival of treated mice and reduced the tumor volume in comparison with group treated with 5-FU alone [41].

2.1.2. DNA damage and its determination-*in vivo* studies

When styrene-specific N-7- and O^6-guanine adducts along with adducts of haemoglobin were determined in mice blood, liver, lungs and spleen, we found a clear dose-response relationship for all adducts. 7-Alkylguanines, formed in higher extent than O^6-guanine adducts, were most abundant in lungs. In this study we demonstrated for the first time the formation of DNA adducts after intraperitoneal administration of styrene *in vivo* [42]. By examining genotoxic effects of styrene in a subacute inhalation study in mice

we observed that 7-SO-guanine adducts in mice lungs were 40-times more abundant than those of 1-SO-adenine adducts, both adducts strongly correlated with exposure parameters. Interestingly, neither DNA adducts nor SSBs were detectable after any time interval or any styrene concentration in mice liver, suggesting more efficient DNA repair in the liver than in lungs [43,44]. In a study of similar design, we observed gradual increase in BER capacity during exposure (days 7 and 28 of exposure), reaching a maximum on day 1 post-exposure, followed by a return to control levels. A significant correlation between BER activity and the concentration of 1,3-BD in blood suggested a possible induction of DNA-repair activity by 1,3-BD and its metabolites. Significantly higher frequencies of micronuclei (MN) we recorded during the exposure [45]. Our additional study attempted to assess the quantitative relevance of DNA adducts induced by styrene in mice. A comparison of 7-alkylguanines excreted in urine with 7-SO-guanines in lungs (after correction for depurination and for missing α-isomers) revealed that persisting 7-SO-guanine DNA adducts in lungs account for about 0.5% of the total alkylation at N7 of guanine. The total styrene-specific 7-guanine alkylation accounted for about 1.0×10^{-5}% of the total styrene uptake, while N1-adenine alkylation contributed to this percentage only negligibly [46].

2.1.3. DNA damage and its determination-studies in humans

Since alkylation at the O^6 -position of guanine is considered as a pro-mutagenic lesion, resulting in a GC→AT transition [47], the anticipated stability of these O^6 -SO-guanine adducts pinpointed them as possible sensitive and specific biomarker of both the exposure and the biological effect. We have developed modified nuclease P1 version of ^{32}P-postlabelling assay and applied it in samples from lamination workers exposed to high concentrations of styrene. For the first time we proved DNA adduct formation in human lymphocytes of individuals exposed to genotoxic xenobiotics [48]. We subsequently addressed the persistence of O^6-SO-guanine adducts in DNA from lymphocytes (PBL) and granulocytes of hand laminators and control clerks. While minute DNA adduct levels were found in granulocytes, the O^6 -guanine adducts in PBL of laminators were significantly higher than those in controls. The levels of O^6-SO-guanine adducts in hand laminators were remarkably stable, irrespectively of two-weeks interruption of exposure, suggesting slow removal of this DNA damage from DNA [30].

A successful attempt to identify 1-SO-adenine adducts in workers occupationally exposed to styrene has been reported by us in [49]. In another our study we reported O^6-SO-guanine adduct levels and SSBs consistently significantly higher in exposed workers than in controls. The HPRT mutant frequency (MF) was also moderately higher in hand laminators. We concluded that styrene exert genotoxic and possibly mutagenic effects *in vivo*, however, there is no simple quantitative relationship between DNA adducts, HPRT MF and SSBs [50]. In a comprehensive approach to biological monitoring of 44 workers occupationally exposed to styrene we found a significantly higher level of SSBs in mononuclear leukocytes of the styrene-exposed workers compared with unexposed controls, SSBs strongly correlated with years of exposure. The styrene-exposed workers also showed a significantly increased frequency of chromosomal aberrations (CAs). The proliferative response of concanavalin A stimulated T-lymphocytes was significantly suppressed in workers exposed to styrene, whereas the percentage of monocytes was enhanced in the exposed group. Flow cytometry disclosed an increased expression of adhesion molecules CD62L, CD18, CD11a, CD11b, CD49d and CD54 in the exposed workers [51]. Detailed analysis of immune parameters revealed altered cell-mediated immune response of T-lymphocytes and imbalance in leucocyte subsets in peripheral blood of workers exposed to styrene [52]. We have followed multiple biomarkers of styrene exposure and genotoxicity in lamination workers and controls during 3-year period in six consecutive samplings. O^6-styrene guanine adduct levels were significantly higher in the exposed group as compared to controls and significantly correlated with haemoglobin adducts, SSBs and years of employment. Styrene-induced N-terminal valine adducts correlated strongly with external exposure indicators, DNA adducts and HPRT MF. The styrene-exposed group exhibited significantly higher SSBs than the control group; SSBs correlated with indicators of external exposure and with O^6-styrene guanine adducts, but not with haemoglobin adducts or HPRT MF. Our data from repeated measurements of the same population over a 3-year period suggest possible mechanisms of genotoxic effects of styrene and the interrelationship of individual biomarkers [53]. Biological significances of specific DNA adducts and their role in the cascade of genotoxic events have been reviewed in [1]. Styrene genotoxicity and possible carcinogenicity may be mediated by the oxidation of the arene moiety of styrene. The relevance of this metabolic route *in vivo* was studied

by the determination of urinary 4-vinylphenol metabolites. Although this metabolic pathway accounted for about 0.5–1% of styrene metabolism, it is capable to induce arene oxide adducts in humans [54]. We have also investigated genotoxic effects of another proven human carcinogen, 1,3-BD, which occurs in tire production. Increased levels of SSBs, CAs and MN were recorded in exposed workers as compared to controls [51]. One year later we analysed BD-induced specific N1-(2,3,4-trihydroxybutyl) adenine (N-1-THB-Ade) adducts in PBL of workers occupationally exposed to butadiene (BD) by ^{32}P-post-labelling using HPLC with radioactivity detection. This study showed for the first time BD-induced DNA adducts in humans and suggested their feasibility as a biomarker in human biomonitoring [55]. The tire plant works we further investigated in relation to their genetic background, comprising single nucleotide polymorphisms (SNPs) in genes encoding biotransformation and DNA repair enzymes. We have documented that exposed individuals in the tire production, who smoke, exhibit higher CAs frequencies, and the extent of chromosomal damage may be modified by relevant SNPs [56].

2.2. DNA repair tests

2.2.1. Method development and *in vivo* studies

Since individual DNA repair capacity (DRC) emerges as one of the most complex biomarkers and integrates factors such as gene variants, gene expressions, the stability of gene products, the effect of inhibitors/stimulators, lifestyle and environmental factors, it is of key importance in the identification of cancer risk, disease prognosis, progression and therapy prediction [57]. Functional DNA repair assays provide fundamental information about the capacity of the organism to cope with chronic exposure to numerous environmental and dietary genotoxicants. Since DRC represents a complex marker for functional evaluation of multigene DNA repair processes in cancer onset with future prospects in personalized prevention and/or cancer treatment, we dedicated considerable effort to the functional evaluation of DNA repair in human biopsies and its relation to other cellular biomarkers [58].

2.2.2. DNA repair capacity determination in humans

In a comprehensive study we evaluated DRC in both styrene-exposed and control groups. DRC increased with the exposure, except for the group exposed to the highest styrene concentration. In this particular group, increased DRC to remove oxidative DNA damage was recorded [59]. In a study employing the functional assay for measuring DRC, we observed relationship between DRC and polymorphisms in XRCC1 and XPC genes in healthy subjects. SNP in XPD gene affected the frequency of CAs [60]. Our earlier study was suggestive of the relationship between BER gene variants and DRC responsible for removing oxidative DNA damage [61]. In another cohort of styrene-exposed and control individuals, the BER DRC and the repair rates of 8-oxoguanines were investigated. Most importantly, we found a negative correlation between all exposure parameters and SSBs. The positive correlation between exposure parameters and DNA repair rates suggested that particular DNA repair pathways may be induced by styrene exposure [62]. We have also investigated secondary oxidative stress associated with styrene exposure. We concluded that styrene exposure seemed to be associated with oxidation damage to nucleic acids, particularly to RNA and with modulation of the BER system [63]. To verify our previous findings on negative correlation between styrene concentration and levels of SSBs reflecting DNA damage in contrast to a dose-dependent increase in the BER capacity, we conducted another study. We recorded again a significant negative correlation between SSBs and styrene concentration at workplace. The BER capacity was the highest in the low exposure group, followed by high exposure group and controls [64]. In the same cohort of styrene-exposed workers and control individuals we found possible relationships between styrene exposure, DNA damage and transcript levels of key cell cycle genes [65]. We investigated genotoxicity in tire plant workers in relation to the capacity of BER in PBL. Interestingly, two-fold higher irradiation-specific DNA repair rate was found among highly exposed workers. The DRC was also higher in smokers than in non-smokers, and these data along with those obtained in styrene lamination plant suggest induction of DNA repair proteins in response to genotoxic exposure [66]. To generate reference data from cancer-free population, which may constitute background for further investigations on cancer patient, we observed a substantial interindividual variability for examined parameters,

SSBs and NER. DNA damage was significantly affected by gender and alcohol consumption, whereas NER-DRC was associated with family history of cancer. The stratification according to common variants in NER genes showed that DNA damage was significantly modulated by the presence of the variant T allele of XPC Ala499Val polymorphism, while DRC was modulated by the presence of the A allele of DNA damage recognition and repair factor (XPA) G23A polymorphism [67]. Our additional study focused on internal and external factors that underlie inter-individual variability in DNA damage and repair and on dietary habits beneficial for maintaining DNA integrity. Sex, fruit-based food consumption and XPG genotype were factors significantly associated with the level of DNA damage: DNA damage was higher in women, fruit consumption was negatively associated with the all measured DNA lesions, and this effect was mediated mostly by cryptoxanthin and tocopherol. Apparently, genetic and dietary factors modulated DNA integrity and the positive health effect of fruit intake is partially mediated via DNA damage suppression and an increase in DRC [68]. In a set of studies, we assessed DRC in cancer onset with prospects in personalized prevention and/or cancer treatment. Our data revealed that NER-DRC and mRNA expressions are different in CRC patients as compared to controls: patients had a lower NER-DRC and simultaneously higher endogenous DNA damage. Accumulation of DNA damage and decreasing NER-DRC acted as independent parameter strongly associated with CRC. This study provided evidence on altered DRC and DNA damage levels in sporadic CRC patients and proposed the relevance of the NER pathway in this malignancy [69].

3. Individual molecular markers in the light of individual susceptibility

We have hypothesized that SNPs in coding and regulatory sequences may result in subtle structural alterations in DNA repair enzymes modulating cancer susceptibility. Associations between various genetic polymorphisms and intermediary molecular markers involved in the cascade of genotoxic/carcinogenic events thus provide useful information on the modulating effects of genetic polymorphisms, on individual susceptibility towards environmental and occupational carcinogens and on the possible links between DNA repair polymorphisms and individual DNA repair rates. We evaluated the data on SSBs, frequency of CAs and HPRT MF in PBL with genotypes of the xenobiotic-metabolising enzymes. Frequencies of CAs were higher in individuals with low and medium activity EPHX genotypes. This study confirmed that markers of individual susceptibility may provide a tool for individual genotoxic risk assessment [60,62,70]. Our another results in workers occupationally exposed to 1,3-BD suggested that DNA adducts serve as a sensitive and specific biomarker, integrating exposure and host metabolic capacity, although the data were limited to a small number of subjects [71]. Our further study on tire plant workers demonstrated the importance of evaluating markers of individual susceptibility (SNPs), since they may modulate genotoxic effects induced by occupational exposure to xenobiotics [66]. We have also observed that immune markers in styrene-exposed individuals and immunotoxic responses to environmental and occupational exposures to xenobiotics may be modulated by DNA repair gene polymorphisms and cyclin D1 polymorphism [72]. In the study of Naccarati et al. we investigated for a first time the interactions of polymorphisms in genes encoding xenobiotic metabolizing enzymes and DNA repair genes on the level of DNA damage in humans. We observed modulatory effects of binary gene-gene interactions on SSB levels and demonstrated for a first time that rather a combination of genotypes than single variant modulates the biological processes [73]. We have also attempted to address the association between polymorphisms in DNA repair genes and BER capacity in a healthy population. In brief, gene variants in BER genes XRCC1, hOGG1 and APE1 modulate significantly corresponding BER capacity in healthy individuals [74].

3.1. Chromosomal instability

Existing evidence suggests that the majority of human cancers arise from cells unable to maintain genomic stability, often due to altered DNA repair mechanisms [75]. Structural CAs arise due to direct DNA damage (e.g. ionizing radiation, free radicals) or due to replication on a damaged DNA template, in both cases DNA repair is a key player. The lesions DSBs are mainly responsible for chromosome-type aberrations (CSAs), whereas chromatid-type aberrations (CTAs) arise due to DNA lesions generated by genotoxic damage during G0 phase, which are insufficiently repaired prior the entering of the cell into S-phase [76].

Due to the lack of studies on incident cancer patients, we investigated chromosomal damage in newly diagnosed cancer patients and healthy individuals. The frequencies of aberrant cells (ACs) and CAs were significantly higher in patients as compared with controls. By stratifying patients for distinct neoplasia, markers of chromosomal damage were significantly enhanced in patients with breast (BC), prostate and head/neck cancers, whereas no effect was recorded in patients with gastrointestinal cancers [77]. The aim of this study was to prove that increased CAs in PBL may predict cancer risk, as shown in prospective studies. Strong differences in distributions of ACs, CAs, CTAs and CSAs were observed in lung and BC patients as compared to healthy controls. Binary logistic regression, adjusted for main confounders, revealed that the analysed cytogenetic parameters along with smoking were significantly associated with BC and lung cancer risks. There was no association of chromosomal damage with any clinico-pathological characteristics of studied cancers [78]. We evaluated the association between frequencies of total CAs, CTAs and CSAs, and occupational exposures to volatile anaesthetics, antineoplastic agents, and formaldehyde among 601 medical professionals. Our findings indicated that the presence of genotoxic compounds in operating rooms, oncological units, and pathological departments results in a significant increase in chromosomal damage (impair of chromosomal integrity) among medical workers employed in these facilities [79]. DNA and chromosomal damage (by the lymphocyte cytokinesis-block micronucleus (CBMN) assay) in medical workers exposed to anaesthetic gases was critically reviewed by us [80]. In 730 healthy individuals we observed that the cyclin D1 splice site polymorphism is associated with an increased frequency of lymphocyte CAs. The biology of the splice site variant is consistent in

assigning allele A, encoding isoform 1b, with an increased CA frequency as this isoform lacks DNA damage response. We provided here the first evidence on a genetic control of the overall CA frequency [81] and extended this premise in [82]. It is assumed that the frequency of CAs is associated with the risk of cancer, but the causes of CAs in general population are unknown. We have therefore tested whether variants in metabolic genes associate with CAs in healthy volunteers and provided evidence that variants in genes coding for metabolic enzymes, which individually have small effects, interact and are associated with CA frequencies in PBL of healthy volunteers [83]. Since DNA repair plays important role in structural CAs, we investigated functional variants in DNA repair genes in relation to CAs, CTAs and CSAs in healthy individuals. Although individual variants in genes encoding DNA repair proteins modulate CAs only modestly, several gene–gene interactions in DNA repair genes evinced either enhanced or decreased CA frequencies suggesting that CAs accumulation requires complex interplay between different DNA repair pathways [84]. Chromosomal integrity is also ensured by the mitotic checkpoint machinery. In view of their importance we studied variants in main checkpoint related genes in relation to CAs. Genetic variation in individual genes played a minor importance, consistent with the high conservation and selection pressure of the checkpoint system. However, gene pairs were significantly associated with CAs. Apparently gene variants at different checkpoint functions seemed to be required for the formation of CAs [85]. Within study of Niazi we have conducted a genome-wide association study (GWAS) on 576 individuals with data on CAs, followed by a replication in two different sample sets (replication 1 and replication 2). Altogether 11 loci reached the P-value of 10^{-5} in the GWAS. These loci were associated with genes involved in mitosis, response to environmental and chemical factors and genes involved in syndromes linked to chromosomal abnormalities. Identification of new genetic variants for the frequency of CAs offers prediction tools for cancer risk [86]. Further, we have conducted two GWASs on healthy individuals in the presence and absence of genotoxic exposure. We identified five loci with in silico predicted functionality in the reference group and four loci in the exposed group, with no overlap between the associated regions. In the reference group loci within genes related to DNA damage response/repair were identified. Other loci identified in both groups are involved in the segregation of chromosomes and chromatin modification [87].

4. Cancer epidemiology

4.1. High and low penetrance genes, environmental and microenvironmental factors

The complex aetiology of malignancies, comprising genetic factors, life-style, environmental exposure and microenvironment, has been pinpointed [4,88,89].

Cancer is a complex disease with multi-mechanistic and multifactorial aetiology, comprising genetic, environmental (life-style) and microenvironmental factors [4]. The complex biology of genomic instability is involved in malignant transformation [17]: this includes telomere homeostasis [90], random mutations arising during DNA replication of non-malignant stem cells [91], maintenance of proper balance of DDR pathways to ensure favourable response of organism towards DNA damaging agents [92], induction of low-fidelity compensatory alternative DNA repair, causing mutations, by microenvironmental stress or microbiota directly [93,94] and complex interactions triggered by inflammation of various aetiology [95]. Interestingly, every DDR process was functionally impaired to some extent in one or more cancer types [96]. This is pronounced in familial cancers with known high penetrance germline mutations in DNA repair genes: tumor suppressor Breast Cancer 1 and 2 genes (BRCA1/BRCA2) in BC, MMR and polymerase deficiency (MutL homolog 1-MLH1, MutS homolog 2-MSH2, MutS homolog 6-MSH6, PMS1 homolog 2 and DNA polymerase ε genes) in CRC and ovarian cancers (OC), deleterious mutations in radiation-repair genes RAD51 paralog C and RAD51 paralog D and breast cancer tumor suppressor 1 (BRCA1) mutation in OC [97–102]. Germline inactivation of BER gene mutY DNA glycosylase (MUTYH) causes colorectal polyposis, resulting in CRC [103]. The hereditary syndromes account for about 2% of all malignancies [89]. However, sporadic cancers with multifactorial aetiology constitute most malignancies. DNA repair mechanisms are important players involved in both cancer initiation and progression [104,105]. A recent study overviewed the involvement of DNA repair and DDR pathways in the onset of cancer, its progression, and patients´ therapeutic response in 33 cancer types. Mutations and loss of heterozygosity were observed in 33% of DNA repair and DDR genes [106]. Due to the importance of DNA repair in the disease development and therapy response, the authors sought for establishing a panel of functional biomarkers that define the DNA repair status of the target tissue [69,107,108].

CRC represent an excellent model of carcinogenesis (from early adenoma to adenocarcinoma) with pronounced inter- and intra-tumor heterogeneity [109,110]. There is emerging evidence for a role of inflammation, oxidative stress and metabolic dysfunction as underlying, interactive mechanisms in CRC. The impact of short- and long-term dietary and lifestyle exposures on the gut microbiome, and its impact on colonic homeostasis have long been suspected but are only now beginning to be explored. Lifestyle factors such as obesity, physical inactivity or alcohol drinking may affect CRC development, treatment efficacy and overall survival (OS). Individuals with severe defects in DNA repair are at greatly increased risk of cancer and other diseases. The cascade of events from the initial exposure to (pro)carcinogens via the maintenance of genome integrity, cancer risk, disease progression, prognosis and therapy outcome and whether these processes are controlled for genetically, epigenetically or otherwise are the main issues of the following chapters. By hypothesizing that the individual genetic background modulating the DRC affects the susceptibility to cancer, we reviewed and evaluated the studies investigating an influence of DNA repair polymorphisms on the risk of sporadic CRC and/or adenoma. We highlighted the need to analyse genotype combinations/interactions in sufficiently large numbers of patients and controls as well as to associate gene variants to particular tumor localization/CRC phenotype [111]. We anticipated that functional polymorphisms in the genes involved in insulin pathway (INS), insulin receptor (INSR), insulin-like growth-factor binding protein 1 (IGFBP1), insulin receptor substrate 1 (IRS1), and insulin receptor substrate 2 (IRS2) are associated with CRC. In fact, we found that the INSR A-603G promoter variant was associated with increased risk of CRC, whereas IRS1 variant allele with decreased risk [112]. This study initiated our investigations of various gene variants associated with the risk of various cancers, such as CRC, pancreatic, OC, BC. In our present serologic and Mendelian randomization (MR) analyses we found circulating level of IGF1 associated with CRC risk and its subsite localization. Using genetic data from 52,865 cases with CRC and 46,287 controls, a higher level of IGF1, determined by genetic factors, was associated with increased CRC risk [113]. Our study on 532 patients with sporadic CRC postulated that disease susceptibility is influenced by genetic polymorphisms in the DNA repair system. The analysis of binary genotype combinations showed increased CRC risk in individuals simultaneously homozygous for the variant

alleles of APE1 Asn148Glu and hOGG1 Ser326Cys. We concluded the effect of the single DNA repair polymorphisms on the risk of CRC is subtle [114]. Similar study was carried out addressing association of SNPs in DNA mismatch repair (MMR) genes with the risk of sporadic CRC. Our data showed a limited role for the investigated individual variants in MMR genes for the susceptibility to CRC. The haplotypes covering hMSH6 gene may, however, be involved in risk modulation in this population [115]. We continued with characterizing of epigenetic (CpG promoter methylation) and gene expression profiles of MMR genes in sporadic CRC patients and found the promoter methylation of MLH1 gene in 9% of CRC tissues. We have also recorded different pattern of MMR genes expression according to tumor localization [116]. We evaluated further 15,419 SNPs within 185 DNA repair genes using GWAS within our consortium collaboration. The data revealed that rs1800734 (in MLH1 gene of MMR system) was associated with colon cancer risk and rs2189517 (in RAD51 paralog B, HR repair pathway) with rectal cancer risk. Defects in MMR genes are crucial for familial form of CRC but our findings suggest that genetic variations in MLH1 are important also in the individual predisposition to sporadic colon cancer [117]. The role of variants in MMR genes in the risk and onset of various cancers and the lack of complex interactions of MMR variations with both the environment and microenvironment in the cancer pathogenesis has recently been summarized [118]. By actively exporting a wide variety of molecules from cells ATP-Binding Cassette (ABC) transporters contribute to reduce the local cellular burden of toxic compounds. In our study by exploring 15 tagging SNPs, covering all the known genetic variation of the ABCG2/BCRP gene, we did not find any strong and unambiguous association between these polymorphisms and CRC risk. We did not disclose any significant association between the two ABCC3 polymorphisms and CRC risk either [119]. ABCB1 also eliminates several carcinogens from the gut. By addressing the impact of ABCB1 genetic variants on CRC risk we did not record any SNPs tested being significantly associated with CRC risk in the replication study. In our hands, ABCB1 gene variants play at best a minor role in the susceptibility to CRC [120]. ABC transporters play also a crucial role in tumor resistance by the efflux of anticancer agents outside of cancer cells. We explored transcript levels of all human ABCs in tumours and non-malignant tissues from CRC patients collected before the first line of 5-FU treatment. Most of the studied ABCs were down-regulated or unchanged between tumours and mucosa tissues. There were

differences in gene expressions depending on the tumor localization. Transcript levels of ABCC6, ABCC11, ABCF1 and ABCF2 were significantly lower in non-responders to palliative chemotherapy in comparison with responders [121]. Exome sequencing identified the somatic mutation spectrum of CRC tumors and described up to 140 candidate cancer (CAN) genes. Our hypothesis was that germline variants in these genes influence CRC risk, like adenomatous polyposis coli (APC), which is causing CRC through germline and somatic mutations. Our study disclosed that the studied functional germline variants are unlikely to affect CRC risk or survival [122].

Year 2008 witnessed the large GWAS with our participation as consortium members. Our study confirmed the previously reported 8q24, 15q13 and 18q21 CRC risk loci and identified two previously unreported associations: rs10795668, located at 10p14, and rs16892766, at 8q23.3, which tags a plausible causative gene, EIF3H. Our data provided further evidence for the 'common-disease common-variant' model of CRC predisposition [123]. Using the data from our GWAS [123] we succeeded to refine the location of the causal locus to a 60 kb region and screened for coding changes. The absence of exonic mutations in any of the transcripts (FLJ45803, LOC120376, C11orf53 and POU2AF1) mapping to this region makes the association likely to be a consequence of non-coding effects on gene expression [124]. By further exploring GWAS we recorded that the CRC risk increased significantly with an increasing number of risk alleles in seven genes involved in MAPK signalling events [125]. GWAS uncovered numerous robust associations between common variants and CRC risk; but only a few concerned proteins altering non-synonymous polymorphisms. This could be due to that non-coding and intergenic variants may change the expression levels of one or several target genes and modulate phenotypic outcomes. Here we overviewed the potentialities to use results from GWAS and expression quantitative loci (eQTLs) studies in the identification and investigation of master regulators in CRC susceptibility [126]. The results from this large, multicentric study illustrated the possibility of decreasing effect with increasing samples sizes. Phenotypic heterogeneity, differential environmental exposures, and population specific linkage disequilibrium patterns may explain the observed difference of genetic effects between investigated cohorts [127]. In a search for genetic variants with the risk on solid cancers, such as CRC, PDAC and BC, we genotyped polymorphisms in the TP53

(rs17878362: A14A2, rs1042522: G4C, rs12947788: C4T, and rs17884306: G4A) gene among patients with above malignancies. In CRC patients, none of the TP53 polymorphisms was significantly associated with CRC risk, but we recorded differential distribution of major haplotypes arising from four polymorphisms in the TP53 gene between cases and controls. The effect of haplotypes in the TP53 gene was similar in colon and rectal cancers [128]. By investigating a role of TP53 polymorphisms in modulating the risk of PDAC, we observed that carriers of the variant C allele of rs1042522 polymorphism were at an increased risk. Similarly as in the above study on CRC, the haplotypes based on TP53 polymorphisms modulated the inherited susceptibility to PDAC [129]. Regarding TP53 haplotypes based on four polymorphisms and the risk of BC, the different haplotype distribution modulated BC risk. Our results documented common genetic features in the susceptibility to BC and gastrointestinal cancers in respect to TP53 variations. In fact, similar haplotype distributions were observed for breast, colorectal, and pancreatic patients in associations with cancer risk [130]. The role of TP53 mutations and germline variants in CRC has been reviewed by us [131].

Obesity (and diabetes) has been related to an increased risk of CRC for long [4]. We investigated CRC risk in association with adipokine genes. Our results documented that variants in the adipokine genes may affect CRC risk in combination with variants in diabetes-related genes [132]. Inflammatory and immune responses play a vital role at different stages of colorectal carcinogenesis. C-type lectins mediate inflammatory/immune responses and participate in immune escape of pathogens and tumors. Our study evaluated the correlation between polymorphisms in three C-type lectin genes and CRC risk and clinical outcome. We showed that SNPs in CD209 may affect CRC risk, while a SNP in REG4 may be a useful marker for CRC progression [133]. Interferons (IFNs) are immune-related proteins produced and released by host cells in response to the presence of pathogens. Our study aimed to examine potentially functional genetic variants in interferon regulatory factor 3 and their receptor genes with respect to CRC risk and clinical outcome. Genetic variation in the IFN signalling pathway genes played a role in the aetiology and survival of CRC, but further studies are warranted [134]. In a continuation of our research, we evaluated the effect of potential

regulatory variants in nod-like receptors (NLRs) on prognosis after 5-FU-based therapy of CRC patients. Nod-like receptors NLRC5 are interferon γ-inducible protein involved in immune surveillance with an impact on cancer survival. Among CRC patients, who underwent a 5-FU-based adjuvant regimen, rs12445252 was associated with shorter OS, according to the dosage of the minor allele T. OS was also decreased for all patients who carried at least one minor allele of rs289747. SNPs in NLRC5 may be used as prognostic markers in CRC patients, as well as for survival in response to 5-FU treatment [135]. Since NLRs are important innate pattern recognition receptors and regulators of inflammation, we explored susceptibility in immune system in relation to CRC risk and prognosis. Five SNPs were associated with CRC risk and eight with survival, however these were not replicated in German and Scottish cohort. We suggested to examine whether regulatory variants instead of coding variants affect the expression of NLRs and contribute to CRC risk and progression [136]. We hypothesized that patients affected by inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis, exhibit an increased risk of CRC. Intestinal microbiota populating the human intestine represents another factor modulating CRC risk. In this scenario, a pivotal role is played by the pattern recognition receptors (PRRs), among which Toll-like receptors (TLRs) recognize different microbe-associated molecular patterns (MAMPs) and/or damage-associated molecular patterns (DAMPs), induce expression of several cytokines, and stimulate activation and differentiation of dendritic cells. We have investigated the influence of potential regulatory variants in these genes on the risk of sporadic CRC. There was nominal association between CRC risk and CGAS rs72960018, CGAS rs9352000 and TMEM173 rs13153461 variants. We recorded nine pair-wise interactions within and between the CGAS, TMEM173, IKBKE, and TBK1 genes. Additional 52 interactions were observed when IFN variants were added to the analysis. Epistatic interactions and a high number of risk alleles play an important role in CRC carcinogenesis, offering novel biological understanding for the CRC management [137].

Ornithine decarboxylase (ODC) is a modifier of adenomatous polyposis coli-dependent tumorigenesis. The G316 > A variant may be associated with recurrence of colorectal adenoma and we examined whether this variant also modifies the susceptibility to sporadic CRC. In our hands the G316 > A functional variant in the ODC gene is unlikely

to make much impact on reducing CRC risk regardless of the reduction in risk found for the recurrence of colorectal adenoma [138]. To prevent DNA damage caused by reactive intermediates, phase II biotransformation enzymes deactivate them. Our results provided an evidence that interaction between metabolic gene variants contributes to colorectal carcinogenesis [139]. We investigated whether genetic variation in CTNNBL1 affects susceptibility to CRC and tested for signals of recent selection. The ancestral alleles of three SNPs were associated with CRC in the Czech cohort, whereas they were less prominent in the family/early onset-based German cohort. Data derived from several databases and statistical tests consistently pointed to a shaping of CTNNBL1 by positive selection [140]. To study physical activity and obesity the GECCO consortium implemented study addressing physical activity and risks of BC and CRC by Mendelian randomisation analysis. The consortium found a potentially causal relationship between higher physical activity levels and lower risks of BC and CRC. The promotion of physical activity is probably an effective strategy in the primary prevention of these commonly diagnosed cancers [141].

Heme oxygenase-1 (HMOX1) and bilirubin UDP-glucuronosyltransferase (UGT1A1) enzymes, involved in bilirubin homeostasis, play a role in the oxidative stress defence. We found significantly decreased CRC risk in patients with UGT1A1*28 allele. A diplotype analysis revealed an increased risk for a specific HMOX1 genotype combination, particularly in males. Substantially lower serum bilirubin levels appeared in CRC patients compared to the controls. UGT1A1*28 allele carrier status mirrored a protective factor against the development of CRC in males, whereas low serum bilirubin levels are associated with an increased risk of CRC in both genders [142]. Mucins and their glycosylation play an important role in colorectal carcinogenesis. We examined potentially functional genetic variants in the mucin genes or genes involved in their glycosylation with respect to CRC risk and clinical outcome. In patients without distant metastasis at the time of diagnosis, two MUC4 SNPs, rs3107764 and rs842225, showed association with OS and EFS after adjustment for age, sex and TNM stage [143]. From dietary components low selenium (Se) status correlates with increased CRC risk. Selenoprotein genes may influence susceptibility to CRC. By analysing 12 SNPs in selenoprotein genes we recorded three SNPs significantly associated with an altered risk

of CRC: rs7579 (SEPP1), rs713041 (GPX4) and rs34713741 (SELS). Our data indicated that SNPs in SEPP1, GPX4 and SELS influence risk of CRC. We proposed that these variants may represent potential biomarkers of CRC risk [144]. It was also postulated that increased levels of vitamin D may protect against CRC development and recurrence. In our hands, none of the four SNPs in vitamin D receptor tested had any significant effect on CRC risk [145].

In our reviews we underlined the importance of genetics, environment/lifestyle and microenvironment in the interplay for the onset and development of sporadic CRC [4,88]. Critical association of gut microbiota with immune response and CRC onset has recently been reviewed by [146]. There is increasing evidence for a role for Fusobacterium nucleatum (F. nucleatum) in CRC development and prognosis. High, compared with low, levels of F. nucleatum in colorectal tumor tissues were associated with poorer OS. However, inclusion of F. nucleatum in risk prediction models did not improve the ability to identify patients who died beyond known prognostic factors such as disease pathology staging. Although the increased presence of F. nucleatum was associated with poorer prognosis in CRC patients, its relevance as a prognostic biomarker is limited [147].

Molecular sensing in the gastrointestinal (GI) tract detects ingested harmful drugs and toxins. Genetic variants affecting these responses may modulate efficiency of the gut to eliminate these threats. TAS2R14 is one of members of the taste receptor family with several polymorphic variants. Substances capable to activate TAS2R14 are powerful toxic and carcinogenic agents. However, we did not find any evidence of significant associations between SNPs in the TAS2R14 gene and CRC risk in the studied population [148]. We also investigated all the common genetic variations of Taste Receptor 2R38 (TAS2R38) gene in relation to CRC risk. We did not find any significant associations between individual SNPs of the TAS2R38 gene and CRC in two populations. The analysis of diplotypes and phenotypes disclosed that the non-taster group had an increased risk of CRC in comparison to the taster group. We recorded a suggestive association between the human bitter tasting phenotype and the risk of CRC in two different populations of Caucasian origin [149]. Above findings inspired us to test the genetic variability of the TAS2R16 gene, encoding the bitter taste receptors that selectively

binds to salicin. We have not disclosed any statistically significant association between CRC risk and TAS2R16 SNPs. We noted that SNPs within TAS2R16 gene do not influence colon cancer susceptibility, but exert a role in rectal cancer [150]. Ghrelin has two major functions: the stimulation of the growth hormone production and the stimulation of food intake. Accumulating evidence also indicates a role of ghrelin in cancer development. We have identified two SNPs associated with lower risk of CRC, namely SNPs rs27647 and rs35683, the T allele of rs27647 SNP exerted a moderately protective effect [151].

The consortium COGENT (COlorectal cancer GENeTics), in which we participated for long, has set up the rationale for identifying low-penetrance variants for CRC and spelled out the difficulties in conducting statistically and methodologically rigorous studies and follow-up analyses [152]. By GWAS of CRC we have identified two genomic regions in which pairs of tagging-SNPs are associated with disease; these comprise chromosomes 1q41 (rs6691170, rs6687758) and 12q13.13 (rs7163702, rs11169552). The authors suggested the use of post-GWAS fine-mapping studies as challenging in identifying candidate functional variants in at least some cases [153]. In the frame of COGENT again, we attempted to identify predisposing loci in patients with familial CRC and polyposis, since a substantial fraction of heritability is still unexplained. Homozygosity mapping revealed a disease-associated region at 1q32.3 which was part of the linkage region 1q32.2–42.2 identified in the CRC family. Sequencing identified the p.Asp1432Glu variant in the MIA3 gene (known as TANGO1 or TANGO) and 472 additional rare, shared variants within the linkage region. Immunohistochemistry revealed increased expression of MIA3 in adenomatous tissues [154]. The genetic architecture of CRC was further studied within GECCO consortium on the whole-genome sequencing of 1,439 cases and 720 controls, imputation of discovered sequence variants and Haplotype Reference Consortium panel variants into GWAS data, and on testing for association in 34,869 cases and 29,051 controls. We discovered a strongly protective variant signal at CHD1. In a combined meta-analysis of 125,478 individuals, we identified 40 new independent signals at $P < 5 \times 10^{-8}$, bringing the number of known independent signals for CRC to ~100. New signals implicate lower-frequency variants, Krüppel-like factors, Hedgehog signalling, Hippo-YAP signalling, long noncoding RNAs and somatic drivers,

and support a role for immune function in CRC. These analyses suggested that CRC risk is highly polygenic [155]. Additional GECCO consortium study addressed early-onset CRC (below 50 years of age), which is increasing in incidence. We have investigated a polygenic risk score (PRS) based on 95 CRC-associated common genetic risk variants in association with risk for early-onset CRC. In an analysis of associations with CRC per standard deviation of PRS, we found the cumulative burden of CRC-associated common genetic variants to associate with early-onset cancer. Analyses of PRS, along with environmental and lifestyle risk factors, might identify younger individuals who would benefit from preventive measures [156]. PRS was further explored construct accurate CRC risk prediction models. We derived and compared different approaches to generating predictive PRS from GWASs on 55,105 CRC cases and 65,079 controls of European ancestry. Our consortium effort added to a risk-stratified CRC screening and targeted interventions [157].

4.2. Epigenetic regulations in solid cancer

Colorectal carcinogenesis is a multistep process involving the accumulation of genetic alterations over time that ultimately leads to disease progression and metastasis. However, binding of transcription factors to gene promoter regions alone cannot explain the complex regulation pattern of gene expression during this process. A high grade of regulatory flexibility of gene expression is mediated by chromatin structure. Posttranslational modifications on histone proteins such as acetylation, methylation, or phosphorylation determine the accessibility of transcription factors to DNA. DNA methylation, a chemical modification of DNA that modulates chromatin structure and gene transcription acts in concert with these chromatin conformation alterations. Small non-coding RNAs represent another epigenetic mechanism regulating gene expression. Our recent review provided examples of the different epigenetic players, overviewed their role for epithelial-mesenchymal transition and metastatic processes and discussed their prognostic value in CRC [158]. We conducted the first study on small non-coding RNAs in colorectal carcinogenesis in 2008. We hypothesized that small non-coding RNA molecules such as micro-RNAs (miRNAs), can bind to the 3´-untranslated regions (3´-UTR) of messenger RNAs and interfere with their translation, thereby regulating cell growth, differentiation, apoptosis and tumorigenesis. By that time, we identified fifty-

seven SNPs in miRNA-binding sites and disclosed significant associations between risk of CRC and variant alleles of CD86 and INSR genes [159]. In this study we observed significant associations between the risk of CRC and the variant alleles of KIAA0182 (rs709805) and NUP210 (rs354476) genes. Our results highlighted the importance of SNPs within miRNA-dependent regulatory regions [160]. Here we sought for a coordination between genes involved in DNA repair pathways and post-transcriptional gene regulation by miRNAs. We investigated the role of genetic variations in miRNA-binding sites of NER genes in association with CRC risk and observed that rs7356 in RPA2 and rs4596 in GTF2H1 were associated with CRC risk, but the significance was pronounced in rectal cancer [161]. We addressed SNPs in miRNA-binding sites in genes involved in CRC (miRSNPs; i.e. rs1804191, rs397768, rs41116 in APC; rs1137918, s227091, rs4585 in ATM; rs712, rs1137282, rs61764370 in KRAS; rs8674 in PARP1 and rs16950113 in SMAD7). rs8679 within PARP1 was associated with CRC risk and patients' OS. The CC genotype in rs8679 was associated with an increased risk of recurrence/progression in patients with 5-FU-based chemotherapy. Here we provided the evidence that variations in miRNA-binding target sites in the 3'-UTR of PARP1 gene modulate CRC risk and prognosis after therapy [162]. Another epigenetic player in tumorigenesis is represented by long non-coding RNAs (lncRNAs). We have analysed HOTAIR lncRNA (Homeobox Transcript Antisense Intergenic RNA) expression levels in tumor and blood of incident sporadic CRC patients in relation to their OS. CRC patients had higher HOTAIR expression in blood than healthy controls, whereas there was no difference in HOTAIR levels between tumor and adjacent mucosa of CRC patients. High HOTAIR levels in tumors were associated with higher mortality of patients. Upregulated HOTAIR relative expression in primary tumors and in blood of CRC patients is associated with poor prognosis of the disease [163]. In this study we focused on nine lncRNAs (ANRIL, CCAT1, GAS5, linc-ROR, MALAT1, MIR155HG, PCAT1, SPRY4-IT1 and TUG1). Our results suggested that changes in expression of lncRNAs between tumor and adjacent mucosa could be used as prognostic biomarkers in CRC patients. Further, cancer progression is associated with detrimental system-wide changes in patient tissue, which might govern patient survival even after elimination of tumour or cancerous cells [164]. We analysed genetic variants in coding regions and in miRNA-binding sites in the 3’-UTR of MMR genes on the risk of CRC, prognosis and the efficacy of 5-FU-based therapy. Two

SNPs in MLH3 and MSH6 genes were associated with clinical outcome. Patients carrying the CC genotype for MSH6 rs1800935 (D180D) and not undergoing 5-FU-based chemotherapy showed fewer recurrences. We provided the first evidence that variations in potential miRNA target-binding sites in the 3'-UTR of MMR genes modulate CRC prognosis and predict therapy [165]. We summarized acquired experience with gene variants in non-coding RNA genes and their target sites as risk factors of sporadic CRC in the review article [166]. The onset and progression of CRC involves a cascade of genetic and/or epigenetic events. We addressed the DNA methylation status of genes relevant in colorectal carcinogenesis and its progression, such as those mutated in CRC (e.g. DNA repair and Wnt signalling pathways). Significantly aberrant methylation was found in 23 genes. There was a good correlation between mRNA expression and methylation status. Aberrant methylations of the DCLRE1C and GPC6 genes were presented for the first time [167]. The subsequent study reported a genome-wide search for novel methylation biomarkers in the rectal cancer. We found significantly aberrant methylation in 33 genes. A validation of results by pyrosequencing provided a good agreement. The BPIL3 and HBBP1 genes were hypomethylated in rectal cancer, whereas TIFPI2, ADHFE1, FLI1 and TLX1 were hypermethylated [168].

We addressed also the effect of SNPs in two miRNA-encoding genes with importance in patients with stage III CRC, treated with 5-FU-based chemotherapy. Carriers of the variant T allele in rs213210 and receiving 5-FU chemotherapy exhibited a worse OS and an increased risk of relapse. The study confirmed that variations in miRNA-encoding genes and thus affecting posttranscriptional regulations modulate CRC prognosis and predict therapy response [169]. Genetic variations in miRNA binding sites located in mucin genes may modulate the maintenance of genomic stability ultimately affecting cancer susceptibility, efficacy of chemotherapy and OS. Mucin genes reflect also adverse prognosis. Patients carrying the CC genotype of rs886403 in MUC21 displayed a shorter OS and higher recurrence risk than TT carriers. The observed associations were more pronounced in colon cancer. This was the first study investigating miRSNPs potentially affecting miRNA binding to mucin genes and revealing their impact on CRC susceptibility or patient's survival [170].

5. Genomic instability in cancer, DNA damage, DNA repair and telomere homeostasis and other factors affecting cancer prognosis and therapy outcome prediction

DNA repair processes are involved in both the onset and treatment efficacy of CRC. We performed a candidate gene approach to analyse the association of non-synonymous SNPs in the DNA repair genes with CRC risk and clinical outcome of patients. There were several significant associations of different nsSNPs with OS and clinical outcomes. Only the genes REV3L, POLQ, and NEIL3 were prominently defined as prediction factors in the regression tree analysis. We documented that even subtle alterations in specific proteins of the DNA repair pathways may contribute to CRC susceptibility and clinical outcome [171]. Methylene-tetrahydrofolate reductase (MTHFR) regulates folate metabolism, and influence DNA methylation and synthesis. MTHFR is essential for the response of CRC to treatment with 5-FU. In our study we found that the 677 C > T polymorphism in the MTHFR gene significantly decreased CRC risk in homozygous carriers of the variant allele. We noted also a significantly different distribution of genotypes between cases and controls for the 66A > G SNP in the MTRR gene. There was a moderate difference in the distribution of the TA haplotype between cases and controls; the TA haplotype was associated with a decreased risk for CRC. We showed that the 677TT genotype and the TA haplotype in the MTHFR gene modulated CRC risk [172]. In the latter study we analysed MTHFR/MTRR genotypes in relation to 5-FU-based chemotherapy of CRC patients. Out of six SNPs investigated, the variant 1298 A > C in MTHFR was associated with progression-free survival (PFS). The patients with AC and CC genotypes showed an increased PFS compared with those with the AA genotype. The identification of markers for predicting individual response represent a step in personalized medicine [173].

One of our most important studies on genomic instability in CRC progression was published in Clinical Cancer Research 2012. Here we have, for the first time, evaluated both excision repair capacities in human colon biopsies to study their participation in colorectal tumorigenesis and observed a moderate increase in NER-DRC in tumors. Individual gene expression levels did not correlate with overall DRC, and we did not detect any aberrant methylation of the investigated genes. Our complex analysis showed that tumor cells are not deficient in BER and NER, but rather follow patterns

characteristic for each individual and are comparable with adjacent tissue [107]. Another important contribution in understanding of the role of DNA repair in genomic instability and treatment response to 5-FU investigated the association of SNP in the 3´-UTR of BER genes on the risk of CRC, its progression, and prognosis. We observed that SNPs in the SMUG1 and NEIL2 genes were associated with OS, SMUG1 rs2233921 TT carriers showed two-fold increased OS compared with those with GT/GG genotypes. The association was more pronounced in association with 5-FU–based chemotherapy. Variations in miRNA-binding sites in 3´-UTR of BER genes modulated CRC prognosis and therapy response [174]. Here we sought for the association of SNPs in predicted microRNA target sites of DSBs repair genes with CRC risk and clinical outcome. The variant CC genotype of rs2155209 in MRE11A was strongly associated with decreased CRC risk when compared with the other genotypes. In colon cancer patients, the rs2155209 CC genotype was associated with shorter OS while the TT genotype of RAD52 rs11226 with longer OS when both compared with their respective more frequent genotypes. miRSNPs in DSB repair genes participated in the maintenance of genomic stability and modulated CRC susceptibility and clinical outcome [175]. To explore the causality of DNA damage/DNA repair as prognostic and predictive factors in CRC, we studied the dynamics of DNA repair from diagnosis to 1 yr follow up, and with respect to CRC treatment. NER and BER genes were significantly under-expressed in patients at the diagnosis as compared to controls, in accordance with reduced NER-DRC and increased SSBs. Six months later, there was an increase in NER-DRC, but not in gene expression levels, both in treated patients only. A year from diagnosis, gene expression profiles and NER capacity in all patients were no longer different from those measured in controls. Our results supported a model in which DNA repair is altered as a result of cancer [176]. The DNA-damaging agent 5-FU represents the most commonly used chemotherapeutic drug for CRC patients. DNA lesions associated with 5-FU therapy are primarily repaired by BER and MMR pathways. Our study indicated that BER-DRC in non-malignant adjacent mucosa was positively associated with OS and relapse-free survival. In multivariate analysis, good therapy responders in TNM stage II and III with an elevated BER-DRC in mucosa exhibited better OS. The effect was highlighted by simultaneous presence of a decreased BER-DRC in tumor tissue. We documented that the level of BER-DRC is associated with patients' survival [177]. In our review we demonstrated that DRC

is a complex marker for functional evaluation of multigene DNA repair processes in cancer onset with prospects in personalized prevention and/or cancer treatment. Since systemic cancer therapy is targeted at DNA damage and its repair, a proper understanding of these processes is a key prerequisite for the optimisation of therapy regimens, prediction of therapeutic response and prognosis in cancer patients [5]. Further information on the role of DRC and the treatment of colon cancer and the response of patients to the therapy is in [88]. In another review we addressed the pivotal role of 5-FU in the treatment of many solid cancers, including CRC [178]. ABC transporters are responsible for the efflux of anticancer agents (5-FU) from cancer cells and participate on drug resistance. We identified 14 SNPs in 11 ABC transporter genes acting as eQTLs loci, i.e. whose variation influence the expression of many down-stream genes. The rs3819720 polymorphism in the ABCB3/TAP2 gene was associated with shorter OS in the codominant, and dominant models. The variant allele of rs3819720 polymorphism significantly affected the expression of 36 downstream genes. Screening for eQTL polymorphisms in ABC transporter genes that can regulate the expression of several other genes, may be informative for the response of CRC patients to the 5-FU-based treatment [179]. In context with previous studies, we searched for eQTL variants influencing the expression of many genes. We identified 4 SNPs, defined as master regulators of transcription. Minor allele variant of the rs4846126 polymorphism was associated with poor OS and PFS, patients homozygous for the variant allele showed two-fold increased risk of death and progression. We retrieved from databases that the variant potentially regulates the gene expression of 273 genes including those associated to the CRC patient's response to 5-FU treatment [180]. We addressed the involvement of major 5-FU pathway genes in the prognosis of CRC patients. There was a down-regulation of DPYD and up-regulation of PPAT, UMPS, RRM2, and SLC29A1 transcripts in tumors compared to paired adjacent mucosa of CRC patients. Low RRM2 transcript level was significantly associated with poor response to the first-line palliative 5-FU-based chemotherapy. DPYS methylation level was significantly higher in tumor tissues compared to adjacent mucosa samples. The over expression of several 5-FU activating genes and DPYD down-regulation indicated that chemotherapy naïve colorectal tumors share favourable gene expression profile for 5-FU therapy. Low RRM2

transcript and UPB1 methylation levels represent separate poor prognosis factors for CRC patients [181].

We investigated the potential of circulating cell-free miRNAs as biomarkers of early detection of CRC. We demonstrated that high levels of circulating miR-34a and low miR-150 levels distinguished groups of patients with polyps from those with advanced cancer (AUC = 0.904), and low circulating miR-150 levels separated patients with adenomas from those with advanced cancer (AUC = 0.875). These results gave a clue to identify two circulating miRNAs capable of distinguishing patient groups with different diseases of the colon from each other, and patients with advanced cancer from benign disease groups [182]. By assuming that miRNA signatures are specific for each cancer type and subgroups of patients with different treatment response, we addressed the specific miRNA signature with clinical and therapeutic relevance for rectal cancer. We identified rectal cancer-specific miRNA signature that distinguished responders from non-responders to adjuvant chemotherapy. A bulk of identified miRNAs belonged to the miR-17/92 cluster. Upregulation of miRNA17, -18a, -18b, -19a, -19b, -20a, -20b and -106a in tumor was associated with higher risk of relapse and their overexpression in rectal cell lines stimulated cellular proliferation. Examination of these miRNAs in plasma exosomes showed that their different levels in rectal cancer patients and controls and they correlated with patient's treatment response [183]. In a collaborative study we proved the association of SBSN expression with progressive stages of cancer development, indicating its role in cancer evolution and therapy resistance [184].

5.1. Telomere homeostasis

There is ample evidence that along with direct DNA damage, mechanisms associated with telomere biology are important contributors to formation of CAs and genomic instability [185,186]. Telomeres, tandem G-rich hexanucleotide repeats that are involved in the maintenance of genome integrity, undergo a progressive shortening through successive cell division. Gradual telomeric attrition is due to incomplete DNA replication of a lagging strand. Telomere length (TL) is also affected by the genotoxic effect of environmental and intracellular DNA-damaging agents and anticancer drugs. Telomere shortening correlates with age. Proliferating tumour cells undergo faster telomeric attrition than non-cancerous somatic cells. Telomere shortening can act as

a potent tumour-suppressing mechanism, limiting cells from uncontrolled growth. However, cancers evolve a mechanism to overcome the proliferative barrier, due to telomere attrition through telomerase rejuvenation. The rejuvenated telomerase preferentially stabilises the shortest telomeres and critically short telomeres can lead to the formation of anaphase bridges through breakage–fusion–bridge cycles that contribute to chromosome instability [83]. By addressing pancreatic cancer (PANC) we investigated genetic background of telomere homeostasis. We performed an analysis of genetic variability of the telomerase reverse transcriptase (TERT) and the telomerase RNA component (TERC) genes in 5,550 subjects with PANC and 7,585 controls. A significant association between a variant rs2853677 in TERT and PANC risk was observed. Three additional SNPs in TERT (rs2736100, rs4583925 and rs2735948) reached statistical significance after correction for multiple testing. We documented that the TERT locus is associated with PANC risk through several independent variants. The association with other gastrointestinal malignancies is likely [187,188]. We investigated chromosomal integrity in PBL from newly diagnosed cancer patients, including 47 BC and 44 CRC patients and 90 matched healthy controls. Our data demonstrated that altered DSB repair measured by sensitivity towards mutagen in PBL occurs particularly in colorectal carcinogenesis. Irrespective of cancer type, telomere shortening was associated with a decreased capacity to repair DSB [189]. In the next study we observed that TL in tumour tissues was significantly shorter than that in the adjacent mucosa. Markedly shorter TL was observed in tumours with lower stage than in those with advanced stages. TL was also shorter in tumours at the proximal than at the distal sites of the colon. Patients with a smaller TL ratio between tumour tissues and the adjacent mucosa were associated with an increased OS. Metastasised tumours in the liver had shorter telomeres than the adjacent non-cancerous liver tissue [190]. Finally, we addressed the prognostic relevance TL in patients with cancer in whom CAs have been analysed and clinicopathological and follow-up data assembled. We observed the accumulation of CAs in PBL corresponded to increased susceptibility to BC and lung cancer, while individuals with longer TL were at a higher risk of BC. The present study demonstrated the association between CAs/TL in PBL and the susceptibility, prognosis and survival of patients with BC, CRC and lung cancers [191].

6. Seeking for new biomarkers and Concept of liquid biopsy

We strove over time for the development and implementation of new biomarkers with sensitivity and specificity to describe studied biological processes. The studies relating phenotype/genotype to cancer, such as DNA adducts and cytogenetic damage, have been analysed as end points that may be related to cancer. Further, mutations in oncogenes and tumor suppressor genes were suggested to give clues to the aetiology of cancer [192]. We analysed DNA and haemoglobin adducts, SSBs in DNA, CAs and HPRT MF in styrene-exposed workers in relation to employment time and postulated a role adaptation and/or population selection on the risk assessment of genotoxic styrene in occupationally exposed humans [193]. As concerns novel biomarkers to improve the management of CRC, we aimed at the dissection of plasma- and tissue-based candidate biomarkers for CRC, and at the implementation of a better understanding of their role in tumorigenesis. Several biomolecules, including serotonin, gamma enolase, pyruvate kinase and members of the 14-3-3 family of proteins, exhibited significant changes when comparing malignant versus non-malignant patient samples [194].

A rich source of potential biomarkers for CRC that has only recently been explored is represented by the circulating human transcriptome comprising both coding and non-coding RNA (ncRNA) molecules. The occurrence of RNA species in extracellular vesicles (EVs) may act as a form of distant communication between cells and their higher abundance in association with cancer demonstrated their relevance [195]. In our review we addressed an employment of circulating cell-free DNA (cfDNA) as a most promising tool among all components of liquid biopsy in solid malignancies. We concluded that the cfDNA analysis represents a new biomarker for cancer detection, prognosis determination and prediction of the response to therapy [196]. These non-invasive approaches can complement and improve current strategies for CRC screening and management. The analysis of circulating ctDNA, tumor-derived circulating cells or circulating miRNA in blood and other body fluids has been reviewed in this article with highlighting their advantages and limitations [197]. We also summarized the options of CRC treatment targeting DNA methylations in tumor utilizing their predictive value. The current challenge is to develop therapeutic inhibitors of DNMT. Based on the role of DNA methylation in CRC, the application of DNMT inhibitors was recently proposed for

the treatment of CRC patients, especially in those with DNA hypermethylation [198]. Finally, predicting clinicopathological and molecular biomarkers in liver metastases with CRC primary tumors were summarized by us [199].

7. Conclusions

Despite the knowledge on carcinogens and their role in carcinogenesis, the final biological links bridging the arising DNA damage and cancer onset needs elucidation. Our most recent publications highlighted the importance of monitoring of the DNA damage dynamics and their repair [200,201]. The lack of functional monitoring of DNA repair and DNA damage response prevents proper understanding of their roles in chronic diseases (malignant diseases on one hand, degenerative diseases on the other) [202]. Curiously, both divergent processes share suboptimal dealing with DNA damage formation and repair. Additionally, there is substantial absence of our knowledge on gene-gene and gene-environment interactions. Despite the deepened knowledge on the genomic and chromosomal stability in last decades, their mechanisms are still poorly understood. Further investigations should be dedicated to telomere homeostasis, since it contributes to genomic instability and carcinogenesis by following mechanisms: a) telomere crisis and erroneous end-capping, leading to chromosomal translocations, b) cellular immortality. The complexity of carcinogenesis is additionally underlined by not completely understood involvements of epigenetic regulations. Close collaboration of scientists and clinicians is inevitable in fighting the cancer.

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List of abbreviations

ABC-ATP-binding cassette
ACs-aberrant cells
APC-adenomatous polyposis coli
APE-apurinic endonuclease
ATM-Ataxia telangiectasia
BER-base excision repair
BRCA-Breast cancer tumor suppressor
CAs-chromosomal aberrations
CAN-candidate cancer genes
cfDNA-cell-free circulating DNA
CRC-colorectal cancer
CSAs-chromosome-type aberrations
CTAs-chromatid-type aberrations
ctDNA-circulating cell-free tumor DNA
BC-breast cancer
DDR-DNA damage response
DNMT-DNA methyltransferase
DRC-DNA repair capacity (-ies)
DSBs-double-strand breaks
EFS-event-free survival
EPHX-microsomal epoxide hydrolase
eQTL-expression quantitative loci
EVs-extracellular vesicles
FU-5-fluorouracil
GI-gastrointestinal
GWAS-genome-wide association study
hOGG1-human 8-oxoguanine DNA N-glycosylase 1
HPRT- hypoxanthine-guanine phosphoribosyl transferase
HR-homologous recombination
IFN-interferon
IGFBP1-insulin-like growth-factor binding protein 1
IGF1-insulin-like growth factor 1
INS-insulin
INSR-insulin receptor
IRS1-insulin receptor substrate 1
IRS2-insulin receptor substrate 2
KRAS-Kirsten ras oncogene homolog
lncRNA-long non-coding RNA

MF-mutant frequency
miRSNPs-single nucleotide polymorphisms in miRNA-binding sites
MLH1-MutL homolog 1
MSH2-MutS homolog 2
MSH6-MutS homolog 6
MMR-DNA mismatch repair
MN-micronuclei
MR-Mendelian randomization
MUTYH-mutY DNA glycosylase
NER-nucleotide excision repair
NLRs-nod-like receptors
ns-non-synonymous
OC-ovarian cancer
OS-overall survival
PANC-pancreatic cancer
PBL-peripheral blood lymphocytes
PDAC-pancreatic ductal adenocarcinoma
PFS-progression-free survival
PRS-polygenic risk score
RAD-radiation-repair genes/proteins
SNPs-single nucleotide polymorphisms
SO-styrene-7,8-oxide
SSBs-single-strand breaks
TERT-telomerase reverse transcriptase
TL-telomere length
TNM-tumor nodus metastasis stages (UICC)
TP53-tumor protein P53
UV-ultraviolet
XPD-xeroderma pigmentosum group D
XPG-xeroderma pigmentosum group G
XPC-xeroderma pigmentosum group C
XPA-DNA damage recognition and repair factor
XRCC1-X-ray repair cross complementing 1