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Obesity and cancer: Relevance of DNA damage response

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ABSTRACT

Obesity is a non-communicable, multifactorial disorder that has steadily emerged as one of the major global health concerns. It significantly increases the risk of diabetes, cardiovascular diseases and cancer. In obesity, the accumulation of excess fat causes increase in the circulatory levels of adipose tissue-specific hormones (adipokines) and exacerbates carbohydrate-fuelled metabolic stress. These factors promote oxidative and genotoxic stress, resulting in chronic inflammation. Moreover, obesity-related factors contribute to increase in DNA damage and disrupt the DNA Damage Response (DDR), thereby promoting genomic instability. Consequently, obesity may facilitate a complex, multi-step process of cellular transformation and cancer progression. However, the mechanisms linking obesity-associated DDR alterations to cancer progression are active areas of investigation. Therefore, elucidating these aspects of DDR in obesity could enhance our understanding of the risk assessment and facilitate advancement in treatment strategies for patients with cancers and obesity.

Introduction

Obesity, a metabolic disorder is global health issue, having reached epidemic proportions worldwide. It is characterized by the excessive accumulation of adipose tissue, which can have serious implications for an individual's physical well-being. In obesity, excess adiposity influences oxidative stress, inflammatory status, and levels of circulatory factors along with glucose and lipid metabolism [1,2]. These factors have a direct impact on DNA damage response (DDR), a conventional intricate pathway responsible for repairing DNA damage and maintaining genomic stability under normal physiological conditions. Alterations in DDR due to obesity may lead to the persistence of DNA lesions, as increased DNA damage and decreased DNA repair contribute to the development of obesity-related diseases [3].

The conceptual evolution of DDR started in the early 1930s when Ultraviolet Radiation (UV) and Infrared Radiation (IR) were unexpectedly found to cause DNA damage and mutations due to interactions with the genetic material. During that time, it was also discovered that

Abbreviations: DDR, DNA (Deoxyribonucleic acid) Damage Response; UV, Ultraviolet; IR, Ionizing Radiation; BER, Base Excision Repair; NER, Nucleotide Excision Repair; MR, Mismatch Repair; HR, Homologous Recombination; NHEJ, Non-homologous End Joining; MRN, Mre11 (Meiotic Recombination 11), Rad50, and Nbs1 (Nijmegen Breakage Syndrome) complex; RPA, Replication Protein A; ATM, Ataxia-Telangiectasia Mutated; ATR, ATM- and Rad3-Related; DNA-PKCs, DNA-Dependent Protein Kinases; CHK1/2, Checkpoint Kinases1/2; SIRTs, Sirtuins; PARP, Poly ADP-Ribose Polymerases; WHO, World Health Organization; BMI, Body Mass Index; TNFα, Tumor Necrosis Factor α; IL, Interleukin; SDF, Sperm DNA Fragmentation; OGG, 8-Oxoguanine Glycosylase; H2AX, H2A Histone Family Member X; BRCA1, Breast Cancer Gene 1; PBMCs, Peripheral Blood Mononuclear Cells; HFD, High-Fat Diet; DMBA, Dimethylbenz[a]anthracene; Th1, Type 1 T Helper; IFN, Interferon; TSS, Transcription Start Site; Casp1, Caspase 1; CD, Chow Diet; Ndufb9, NADH Dehydrogenase 1 Beta Subcomplex 9; CRCD, Calorie-Restricted Chow Diet; Pparg2, Peroxisome Proliferator-Activated Receptor Gamma 2; ROS, Reactive Oxygen Species; DNA-PKcs, DNA-Dependent Protein Kinase Catalytic Subunit; ssDNA, Single stranded DNA; ATRIP, ATR-Interacting Protein; SMARCAL1, SWI/SNF (Switch/Sucrose Non-Fermentable) -Related Matrix-Associated Actin-Dependent Regulator of Chromatin Subfamily A-Like Protein 1; DCA, Deoxycholic Acid; Bax, Bcl-2 (B-cell lymphoma-2)-Associated X Protein; NF?B, Nuclear Factor Kappa B; CAP1, Adenylyl Cyclase-Associated Protein 1; GADD45α, Growth Arrest and DNA-Damage-Inducible Protein; TNFR1, Tumor Necrosis Factor Receptor 1; NAD, Nicotinamide Adenine Dinucleotide; DNMT1, DNA Methyltransferase 1; MLH1, Mut (mutator) L Homologs; IF, Intermittent Fasting; CR, Calorie Restriction; DHE, Dihydroethidium; HSP70, Heat Shock Protein 70; HO-1, Heme Oxygenase-1; RYGB, Roux-en-Y Gastric Bypass Surgery; MGMT, O6-Methylguanine-DNA Methyltransferase; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonists; FDA, Food and Drug Administration; EMA, European Medicine Agency; NEIL1, Neil Endonuclease VIII-Like1; Nampt, Nicotinamide Phosphoribosyl-Transferase; NADP, Nicotinamide Adenine Dinucleotide Phosphate.

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organisms possess the capability to repair induced DNA damage [4,5]. This foundational phase marked the inception of the DNA repair field. Subsequent investigations on the stability and repair of DNA were initiated by various groups to explore the role of repair enzymes in bacterial and human cells. Nearly 85 years later, in 2015 *Tomas Lindahl, Paul Modrich,* and *Aziz Sancar* were awarded the Nobel Prize for their contribution towards mapping the repair enzymes such as glycosylase, DNA ligase, Dam methylase, photolyase, and multi-enzyme complex-uvrABC endonucleases [6]. Their work elucidated the underlying mechanisms involved in DNA repair, revealing that defects in these repair molecules can lead to DNA mutations.

DNA damage refers broadly to the addition of chemicals (such as ethyl group, and genotoxic agents), disruption of base, or nicks and breaks in one or both strands [7]. In contrast, DNA repair is a more specialized process, dictated by the nature of the damage. Various repair mechanisms have been identified, including Base Excision Repair (BER), Nucleotide Excision Repair (NER), Mismatch Repair (MR), Homologous Recombination (HR), and Non-Homologous End Joining (NHEJ). BER addresses alteration in bases caused by deamination, alkylation, and while NER corrects bulky adducts. The mismatch repair mechanism eliminates mismatched bases and double-strand breaks are repaired by either NHEJ or HR. However, DDR plays a crucial role in sensing DNA damage and signalling for the recruitment of appropriate repair machinery.

In the human body, each cell encounters thousands of DNA lesions daily, and these are precisely corrected by an efficient DDR [8]. Thus, DDR, a highly coordinated process, is essential for maintaining the integrity of genetic material thereby ensuring normal cellular functions and cell survival. The initiation of the DDR pathway begins when frontline sensor molecules such as the Meiotic Recombination 11 (Mre11), Rad50 and Nijmegen Breakage Syndrome 1 (Nbs1) complex (MRN complex), Replication Protein A (RPA) as well as KU70/80–86, detect DNA damage and subsequently transmit signals to key DDR protein kinases. These kinases include Ataxia-Telangiectasia Mutated (ATM), ATM- and Rad3-Related (ATR), and DNA-Dependent Protein Kinase Complex (DNA-PKCs). Kinases phosphorylate several targets, promoting precise DNA repair and coordinating the repair activities with replication, transcription, and mitosis [9]. They regulate cell cycle progression by targeting checkpoint kinases 1 and 2 (CHK1 and CHK2) (Fig. 1). Subsequently, depending on the severity of DNA damage, cells may undergo growth arrest or apoptosis [10].

The multifaceted role of DDR extends beyond its primary function of sensing and initiating DNA repair. It provides defence against genotoxic insults, fine-tunes protein synthesis, manages protein trafficking as well as their secretion, and contributes to metabolic reprogramming [11]. DDR molecules exhibit a broader significance beyond DNA repair as genetic mutations and alterations in DDR-associated genes have also been linked to various anomalies including obesity, diabetes, cardiovascular diseases, and cancer development [8,12]. Recently, the role of DDR molecules such as ATM, Sirtuins (SIRTs), Poly ADP-Ribose Polymerases (PARP), and P53 in cellular metabolism has been explored highlighting a close relationship between DDR and the metabolic pathways [12]. Among these, the role of P53 protein has been extensively investigated. P53 functions as a transcription factor for genes important in DNA repair and cell cycle regulation [13]. Clinical studies have shown that deletion of the P53 gene impairs DNA repair in the peripheral blood cells of patients with chronic lymphocytic leukaemia [14].

Collectively, the findings suggest that deregulated DDR can lead to the accumulation of DNA damage, potentially contributing to the

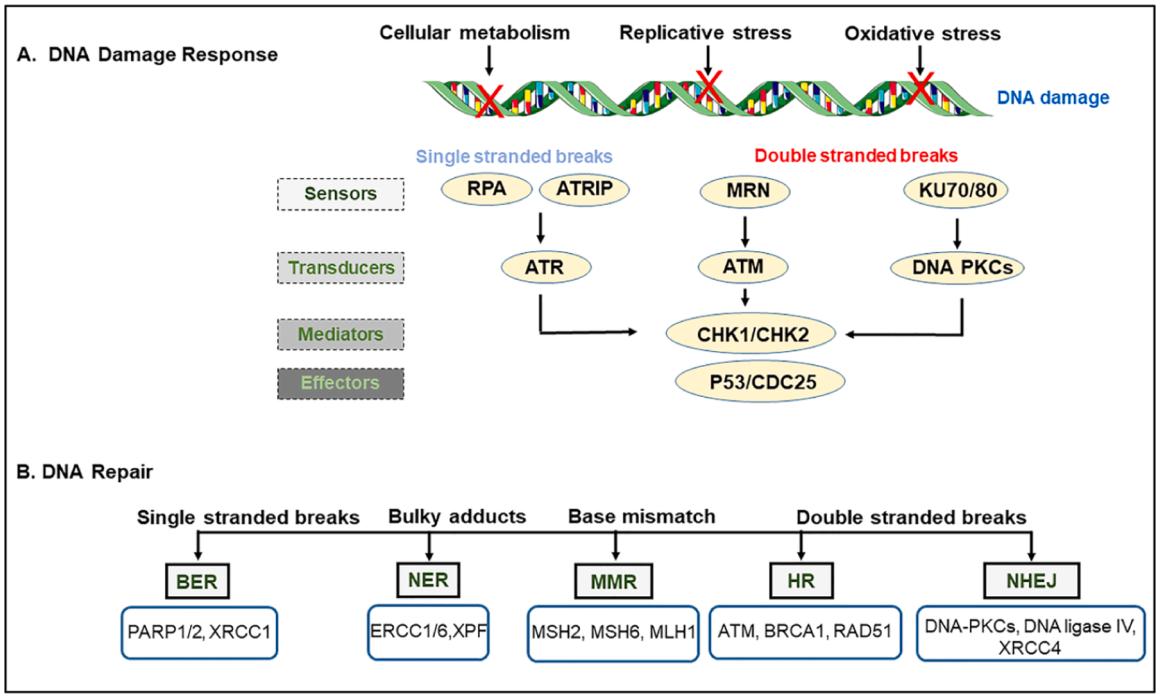

Fig. 1. Schematic representation of molecules involved in DNA damage response and repair. (A) DNA sensors such as RPA, ATRIP, MRN, and KU70/80 sense DNA damage, and transducers such as ATR, ATM and DNA PKCs mediate signalling via effectors P53/CDC25. (B) Depending on the type of DNA damage, the DNA repair machinery BER, NER, MMR, HR or NHEJ is activated.
(RPA, Replication Protein A; ATRIP, ATR-Interacting Protein; MRN, Mre11 (Meiotic Recombination 11), Rad50, and Nbs1 (Nijmegen Breakage Syndrome 1) complex; ATR, ATM- and Rad3-Related; ATM, Ataxia-Telangiectasia Mutated; DNA PKCs, DNA-Dependent Protein Kinase; CHK1/2, Checkpoint Kinases1/2; CDC25, Cell Division Cycle 25; BER, Base Excision Repair; NER, Nucleotide Excision Repair; MR, Mismatch Repair; HR, Homologous Recombination; NHEJ, Non-Homologous End Joining; PARP, Poly Adenosine Diphosphate-Ribose Polymerase; XRCC, X-ray Repair Cross-Complementing Protein; ERCC1, Excision Repair Cross Complementation Group 1; XPF, Xeroderma Pigmentosum Complementation Group F/ERCC4; MSH, Mut (mutator) S Homolog; MLH, Mut (mutator) L Homologs; BRCA1, Breast Cancer Gene 1).

transformation of normal cells into cancerous and supporting their growth. This review primarily focuses on the implications of deregulated DDR in obese disease conditions and its role in the transformation of normal cell to cancerous cell.

Obesity deregulates DNA damage response

A significant proportion of adults and children worldwide are dealing with obesity and overweightness [15]. Obesity is typically defined by an individual's Body Mass Index (BMI) which is calculated by dividing a person's weight (in kilogram) by the square of their height (in meters). According to the World Health Organization (WHO), a BMI of ≥30 is classified as obese, while a BMI of ≥25 is considered overweight. Obesity, a metabolic disorder driven by adiposity is a public health concerns which can lead to serious clinical complications causing a substantial economic burden [16,17]. The excessive accumulation of adipose tissue can cause chronic low-grade inflammation, increased oxidative stress, and alterations in the serum levels of adipokines and hormones (such as visfatin, leptin, resistin, Tumor Necrosis Factor α (TNFα), Interleukin 1β (IL1β), Interleukin 6 (IL-6), apelin, chemerin, omentin, vaspin, adiponectin; insulin and insulin-like growth factors) [18–20]. Obesity also can lead to increase in serum levels of glucose, cholesterol, and triglycerides [21]. Elevated levels of these factors can promote DNA damage and influence the DNA repair mechanisms [3]. Subsequently unrepaired DNA damage can cause mutations, disrupt normal cellular functions due to alterations in expression of crucial genes [7] and contribute to the pathogenesis of various diseases (Fig. 2).

Preclinical and clinical studies suggest that obesity associated biological changes have a detrimental impact on DNA integrity. Clinical study by *Dupont et al.,* indicates that obesity aggravates DNA damage in the sperm [22], potentially impairing spermatogenesis and diminishing male reproductive capability. Notably, Sperm DNA Fragmentation (SDF), a test used to assess male infertility, is increased in obese individuals [23,24]. A meta-analysis study revealed that men with obesity tend to have lower sperm count, decreased sperm concentration and reduced semen volume, all of which contribute to infertility [25,26]. These findings underscore the association between obesity with the impaired male reproductive function, indicating that excessive DNA damage in the sperm may be one of the key mechanisms linking obesity to male infertility.

A study involving hyperphagic mice (obese phenotype) reported an increase in the level of phosphorylated H2AX (serine 139) in small ovarian follicles and enhancement of ATM expression in small and large ovarian follicles compared to the lean control mice. Moreover, obesity was found to alter ATM activation and cleaved caspase 3 levels, a marker of apoptosis, in ovarian follicles, in a stage-specific manner [27]. These results suggest that obesity-induced alterations in DDR vary depending on the maturation stages or ageing of the ovarian follicular cells.

A systematic analysis of 23 independent animal studies revealed that excess body fat induces DNA damage in the brain, liver, colon and testes [28]. Similarly, a clinical study on Italian children with a BMI of ≥ 24 ± 2.8 (indicating overweight or obesity) showed higher levels of phosphorylated H2AX protein and increased frequencies of micronuclei in their Peripheral Blood Mononuclear Cells (PBMCs) compared to the control group. These findings suggest that in individuals, obesity not only elevates risk of DNA damage but also impairs DNA repair mechanisms [29] (Fig. 2).

Recently, *Bhardwaj et al.*, highlighted the consequences of accumulation of DNA damage under obese conditions and its implications in patients with breast cancer carrying *BRCA1* gene mutations. BRCA1 is a critical member of homologous recombination repair mechanism involved in repairing double-stranded breaks in the DNA. The findings revealed a positive correlation between BMI and the accumulation of double-stranded DNA damage in normal breast epithelial cells of

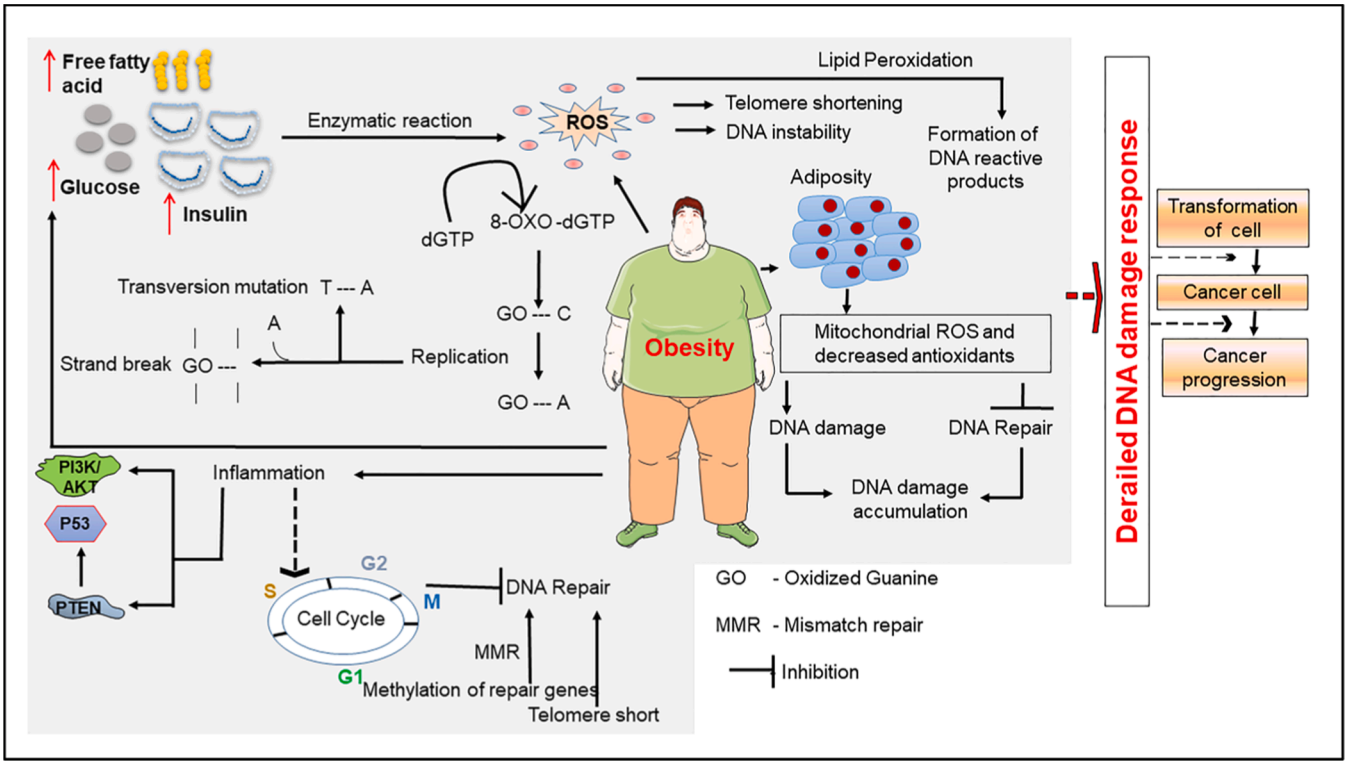

Fig. 2. Impact of obesity-associated physiologies on DNA damage and repair. An increase in free fatty acid, glucose, and insulin may cause oxidative stress, resulting in chromosomal instability. Chronic inflammation and excess adiposity aggravate DNA damage and decrease repair, which may derail DDR. The inefficiency of DDR may have implications for cancer occurrence and progression.
ROS, Reactive Oxygen Species; PI3K/AKT, Phosphoinositide-3-Kinase–Protein Kinase/Ak Strain Transforming; PTEN, Phosphatase and Tensin Homolog Deleted on Chromosome 10.

patients with a mutation in *BRCA1/BRCA2* genes. Furthermore, investigations involving MCF-10A cells with heterozygous mutations in *BRCA1* or *BRCA2* genes cultured in conditioned media derived from the adipose tissue of obese women, compared to those cultured in conditioned media from women of normal weight were undertaken. Interestingly, RNA sequence analysis indicated activation of pathways involved in DNA damage and down-regulation of pathways involved in DNA repair, which suggests that obesity negatively impacts the efficacy of DNA repair pathways, in cells with defective DNA repair machinery. Notably, no significant differences in DNA damage were observed between MCF-10A *BCRA1*$^{+/+}$ cells (wild-type) and MCF-10A *BCRA1*$^{+/-}$ (heterozygous) cells. Additionally, an *in vivo* experiment was performed on mice fed a high-fat Diet (HFD) and exposed to the carcinogen 7,12-Dimethylbenz[α]anthracene (DMBA). An increase in DNA damage was observed in the mammary glands of these mice, which was associated with a higher incidence of breast cancer in *BRCA1*$^{+/-}$ HFD mice compared to those in the control group. These findings support the hypothesis that obesity influences DNA damage response mechanisms, thereby increasing the risk of cancer. It is important to note that the significance of these risk factors may depend on the status of *BRCA1/2 genes* (wild type) in the context of breast cancer without *BRCA1/2* mutation [30].

Obesity promotes accumulation of DNA damage and impairs DNA-repair capacity, thereby increasing genomic instability in affected tissues [31] .

However, in non-obese contexts, excessive unrepaired DNA damage typically triggers a robust DNA-damage response (DDR) that results in cell-cycle arrest and apoptotic elimination of severely damaged cells; whereas, in obesity, pro-survival signalling can weaken this protective mechanism [32].

It has been reported that adipokines and circulating obesity-associated serum factors (for example, leptin, inflammatory cytokines, and lipid-derived mediators) activate canonical pro-survival pathways such as JAK/STAT3, PI3K/AKT/mTOR and Nuclear Factor Kappa B (NFκB), These pathways promote cell growth and survival while reducing apoptosis. The obesity-associated factors also influence DNA repair mechanisms [33].

We therefore hypothesize that in obesity, a combination of (i) increased DNA damage and impaired repair, (ii) chronic pro-survival together with adipokine signalling and (iii) systemic metabolic as well as inflammatory alterations can act together to promote cancer development. Increased DNA damage, deregulated DDR and reduced repair lead to the accumulation and persistence of harmful mutations. Moreover, chronic pro-survival signalling and continuous metabolic or inflammatory support facilitate the survival and growth of damaged cells. Over time, these surviving cells can accumulate additional genetic or epigenetic changes and eventually become tumorigenic.

Altered DNA damage response in cancer

DNA damage and repair mechanisms are diverse and have an important role in the initiation and progression of cancer. Events such as acute changes in cell cycle checkpoints, genetic instability, oxidative stress, chromatin remodelling, by-products of normal cellular metabolism and external factors including ultraviolet, ionizing radiation, and genotoxic agents contribute to mutations and cellular transformation. Moreover, the chemicals that cause cancers in human also promote the development of local and metastatic tumors in experimental animals [34].

Although, the full spectrum of DDR defects is not yet clearly understood, many studies have established a link between DDR dysfunction and development of neoplastic phenotype. For instance, approximately 15% of sporadic colorectal tumors exhibit abnormalities in dinucleotide repeat sequences [35]. Also, 37–55% of patients with

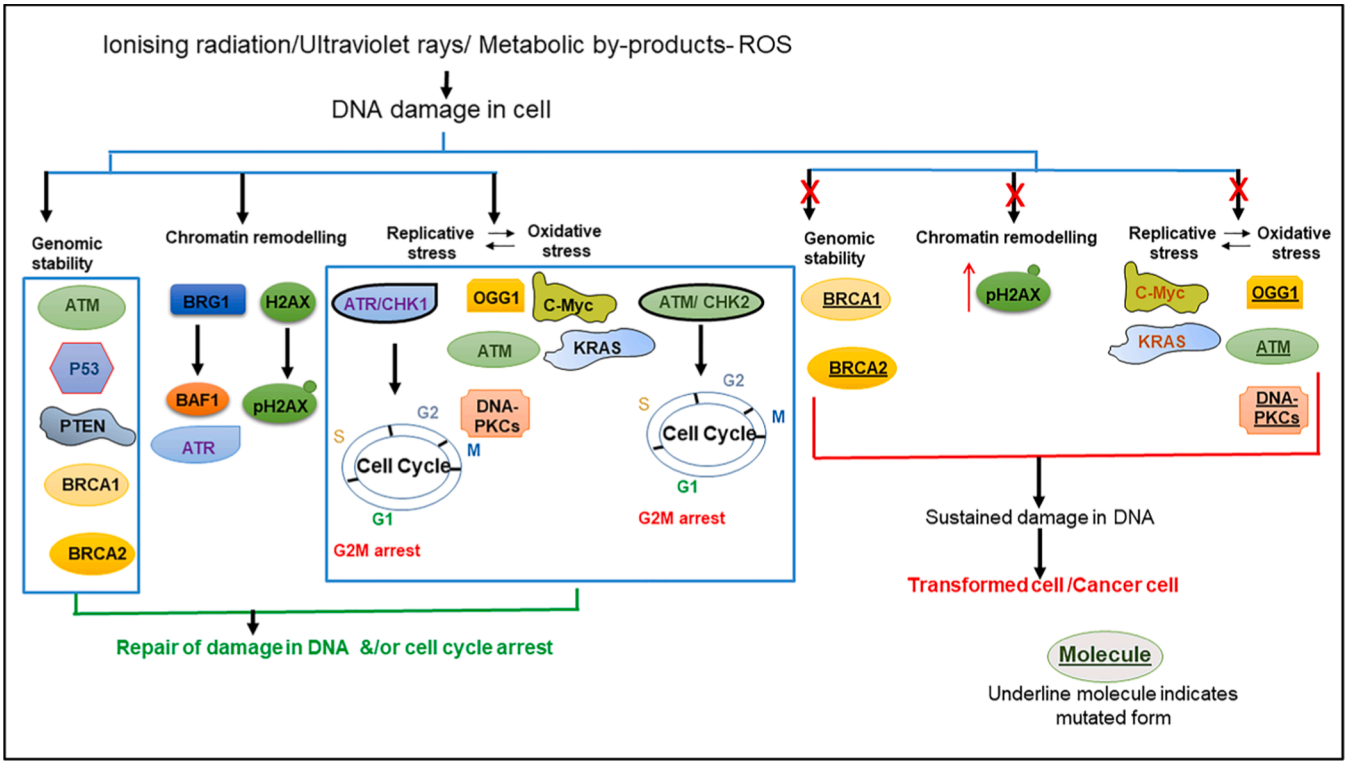

Fig. 3. Pictorial representation of molecules of DDR.
DNA damaging agents cause breaks, nicks, or oxidation of bases, which is taken care of by an efficient DDR. Unrepaired DNA and mutations, up-regulation, or down-regulation of DDR-related genes, may contribute to the sustenance of damage and, eventually, the transformation of cells. (PTEN, Phosphatase and Tensin Homolog Deleted on Chromosome 10; BRG1, Brahma-Related Gene-1; BAF, Brahma-Related Gene-1 Associated Factor; H2AX, H2A Histone Family Member X; pH2AX, Phospho H2A Histone Family Member X; OGG1, 8-Oxoguanine Glycosylase 1; C-myc, Cellular-myc; KRAS, Kirsten Rat Sarcoma Virus).

high-grade serous ovarian carcinoma carry germline or somatic mutations, predominantly in *BRCA1 or BRCA2* genes [36] (Fig. 3).

Studies indicated that excessive oxidative stress generated by cellular metabolism is associated with DNA adduct formation. Oxidative stress is an imbalance between the production of Reactive Oxygen Species (ROS) and the activity of detoxifying enzymes. Additionally, oxidative stress-induced inflammatory responses support cancer cell proliferation, promote angiogenesis, and cause chemo-resistance [37].

During DNA replication in normal cells, the cleavage of residual Single-Stranded DNA (ssDNA) is protected by recruitment of ATR by ATR-Interacting Protein (ATRIP) and Switch/Sucrose Non-Fermentable (SWI/SNF) -Related Matrix-Associated Actin-Dependent Regulator of Chromatin Subfamily A-Like Protein 1 (SMARCAL1) [38]. These events prevent the accumulation of ssDNA and collapsing of replication fork. Moreover, the ATR-CHK1 pathway stabilizes, and repairs damage induced by replicative stress. The oxidative stress-induced ATR/CHK1 axis has been linked to the development of cisplatin resistance in bladder cancer cells and poorer outcomes in breast cancer patients [39,40]. Therefore, inherent or induced down-regulation and overexpression of DDR-related genes may contribute to an increased occurrence of certain cancers and desensitization of cancer cells to chemotherapy. This is likely dependent on the type of cells and stimuli.

Implications of DDR modulated by obesity-associated factors in cancer

In previous sections, the DDR has been discussed in the context of obesity as well as cancer. This section highlights the significance of obesity-associated alterations that may disrupt the DDR in cancer cells under co-morbid conditions.

Metabolism influences DDR by regulating the nucleotide pool, oxidative stress, and methyl–acetyl donors through various pathways. Conversely, DDR also has impact on metabolic pathways thereby, creating a bidirectional and tightly interconnected relationship [11]. This interplay becomes particularly significant in the context of obesity, where in disrupted metabolic state and associated factors may contribute to alteration in DDR.

Obesity, associated with change in adipokine levels and serum factors create a state of chronic inflammation together with increase in oxidative stress. These conditions cause imbalance in DDR, [3,27], deregulate the cell cycle [41], and are associated with the development of cancer [18]. The intricate connection between obesity and cancer is reinforced in a comprehensive study by *Kompella et al.,* [42] in which it has been reported that genetic instability linked to cancer progression is exacerbated by DNA lesions due to oxidative stress in obesity. This phenomenon is further aggravated by lipid by-products such as malondialdehyde, 4-hydroxynonenal, and acrolein. Additionally, secondary bile acids metabolites such as deoxycholic acid (DCA) and lithocholic acid, produced by the gut microbiota in the obese state, act as agents that inflict DNA damage, thereby fuelling the growth of tumor.

The inverse impact of obesity on the efficiency of DNA repair mechanisms contributes to the initiation and progression of cancer [42]. Also, the increased level of DNA damage in obesity-influenced diseases highlights the role of obesity-associated factors in triggering alterations at the DNA or gene level [3]. Therefore, an in-depth study of DDR alterations in the context of obesity and cancer would be valuable for unravelling the role of obesity-associated factors in co-morbid conditions.

Factors such as adipokines, altered gut microbiota, deregulated DDR, and high levels of nutritional factors contribute to DNA damage, which

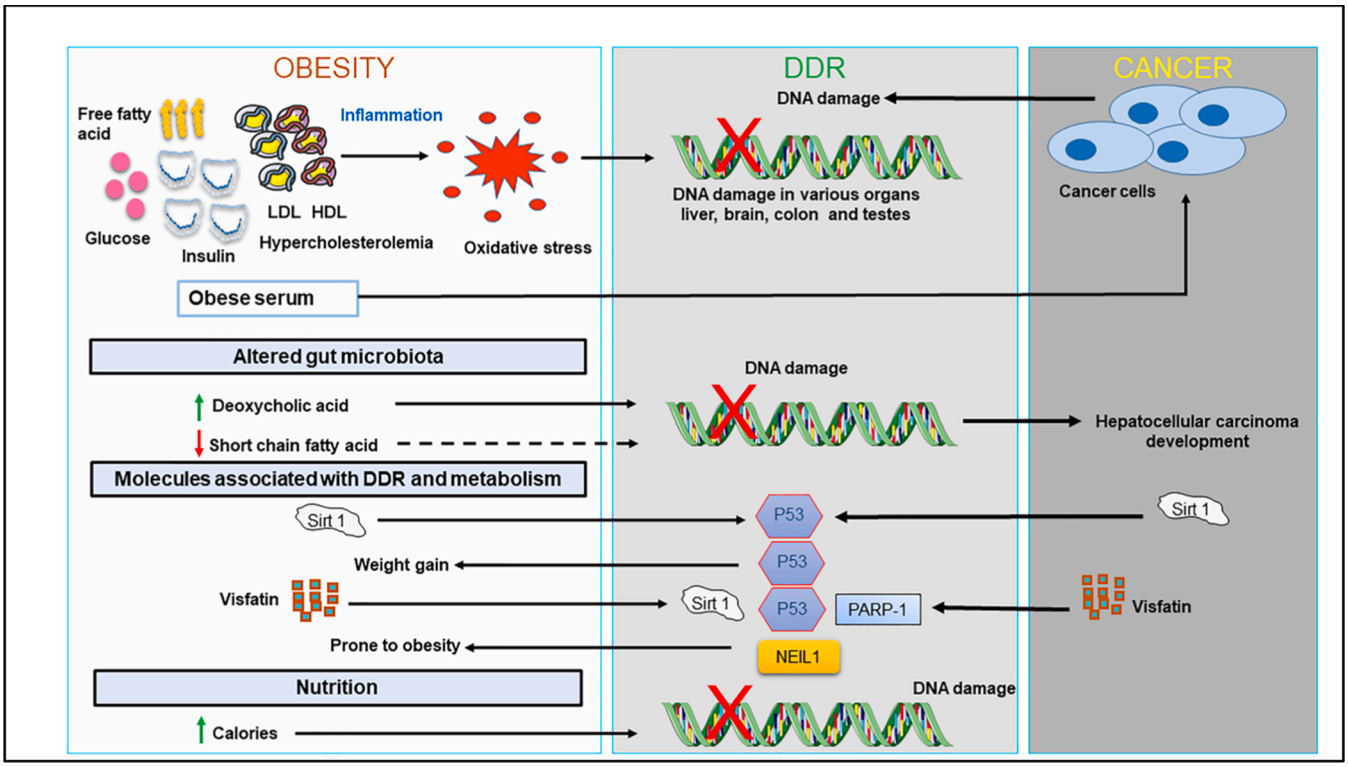

Fig. 4. Parameters altered in obesity, such as elevated levels of free fatty acids, glucose, insulin, cholesterol, and inflammation, promote oxidative stress, which, in turn, interferes with the DNA damage response (DDR) mechanism. Increased concentrations of adipokines in the bloodstream influence the DDR pathway. Simultaneously, increased deoxycholic acid and a reduction in the synthesis of short-chain fatty acids contribute to the accumulation of DNA damage. Crucial molecules like P53, NEIL1, SIRTs, and visfatin have dual roles in both DDR and metabolism, and their levels in obese individuals affect the DDR process. Additionally, a calorie-rich diet exacerbates DNA damage. The inefficiency of DDR mechanisms, either due to the accumulation of DNA damage or decreased repair efficiency, has pervasive consequences, affecting the proliferation, survival, apoptosis, and drug responsiveness of cancer cells.
LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; TNFα, Tumor Necrosis Factor α.

influences cell survival, proliferation, apoptosis, and also the response of cells to chemotherapeutic drugs (Fig. 4).

Adipokines

Adipokines, secreted by adipose tissue, play a crucial role in regulating fat metabolism, energy homeostasis, immune response and reproduction. As signalling molecules, adipokines exert their effect on the cells expressing specific receptors in the liver, hypothalamus, heart, muscle, and other organs including immune cells. An increase in the concentration of circulatory adipokines influences intracellular and extracellular signalling in cells expressing cognate receptors. In cancer cells, the expression of receptors for an adipokines are modulated by the cellular microenvironment and signalling cascades which influences autocrine signalling as well as the interactions between immune cells and cancer cells.

In obesity, altered adipokine levels may promote the proliferation of transformed or normal cells in a cell type-specific manner. For example, differential levels of leptin and adiponectin have been linked to the occurrence and growth of polyps and tumors in carcinogen-induced mouse models of the cancer [43,44]. These studies pinpoint the relevance of adipokines in the cellular transformation and cancer development under obese conditions.

Leptin: Leptin has an important role in regulating energy homeostasis and body weight. Leptin receptors are expressed in the hypothalamus, coronary arteries, and testis. Leptin receptor expression has also been detected in various cancer cells and tumor tissues, including breast cancer (HTB-26 and ZR75–1 cells), liver, and ovarian cancer [45,46]. Leptin exerts a cell type-dependent influence on the DNA damage and repair events. Also, impaired leptin signalling has been implicated in age-associated excessive DNA damage and premature mortality in ob/ob (leptin knockout) and db/db (leptin receptor knockout) mice [47]. Additionally, leptin interferes with histone-to-protamine transition, and increases sperm DNA susceptibility to free radical attacks [48]. In rats leptin treatment is known to aggravate sperm DNA fragmentation [49]. Whereas, in human leukemic cells, leptin reduces DNA damage, enhances DNA repair efficiency, and diminishes the cytotoxic effect of cisplatin, suggesting its role in the chemotherapeutic response [50]. At the DDR level, leptin signalling has been associated with negative regulation of P53 in non-small cell lung carcinoma tissues and endogenous leptin expression has been also shown to promote the proliferation of lung adenocarcinoma cells [51].

The effects of leptin on DNA integrity are not only dependent on the type of cell, but also on the presence of its receptors, the metabolic state of the cells, as well as any concurrent chemotherapeutic treatment. In germ cells (especially in spermatogenesis), leptin not only increases oxidative stress (via ROS) but also disrupts chromatin remodelling, for example by impairing the histone-to-protamine transition [52,53]. Moreover differences in redox balance and NAD^+ levels between cell types may also determine whether leptin causes damage or promotes survival. In leukemic and other hematologic malignancy cells, leptin has been reported to activate JAK2/STAT3 and PI3K/AKT signalling, which are linked to cell survival and anti-apoptotic functions [54]. Overall, beyond its role in energy regulation, leptin can influences DNA damage and repair in a cell and context-dependent manner.

Adiponectin: This adipokine plays a crucial role in regulating lipid as well as glucose metabolism and insulin sensitivity. Adiponectin receptors are present in the liver, skeletal muscle, breast epithelial cells. Their expression has also been detected in various breast cancer cells (MCF7, T47D, MDA-MB-231, MDA-MB-361, and SKBR-3). In cancer cells, adiponectin, primarily through the activation of AMP-activated protein kinase (AMPK) causes growth arrest (G0/G1 cell cycle arrest. This process involves the tumor suppressor protein P53 and the pro-apoptotic protein B-Cell Lymphoma-2 (Bcl-2)-Associated X Protein (Bax). Additionally, adiponectin also modulates the immune response by inhibiting the NFκB through increase in the expression of IL-6, IL-10, TNFα, and IFNγ cytokines in monocyte-derived cells. Importantly, among its various functions, adiponectin also exhibits growth suppressor activity [55].

Adiponectin levels are significantly downregulated in obesity. The reduction compromises its functionality as a cell growth suppressor, thereby creating a favourable environment for the proliferation of transformed cells.

Resistin: Resistin functions as a pro-inflammatory cytokine and regulates glucose and lipid metabolism. Its receptors are present in the monocytes and adipose tissue. Interestingly, expression of one of the receptors for resistin, Adenylyl Cyclase-Associated Protein 1 (CAP1), is detected in patient-derived breast cancer cells [56]. In the context of DDR regulation, overexpression of resistin in mouse cardiomyocytes has been linked to down-regulation of DDR due to reduction in the expression of growth arrest and DNA-Damage-Inducible Protein (GADD45α) [57]. Furthermore, treatment of porcine ovarian cells with resistin has been shown to inhibit DNA fragmentation and caspase activity thereby reducing apoptosis [58]. In vascular smooth muscle cells, resistin decreases the expression of P53, P21, and P27 [59].

Resistin promotes adhesion properties in HCT-116 ($P53^{-/-}$) and SW-48 ($P53^{+/+}$) cancer cells by activating the NFκB pathway, independent of P53 [60]. Notably, serum resistin levels are elevated in obesity-influenced cancers, such as breast and colon cancers. However, resistin levels are also higher in lung and renal cancers, regardless of obesity. Resistin is associated with tumor progression, promotion of angiogenesis, and increase in metastasis in various cancer models [61]. Collectively, resistin in a cell type-dependent manner induces growth arrest or promotes proliferation.

Tumor Necrosis Factor Alpha (TNFα): TNFα is synthesized by monocytes, macrophages, and adipocytes. It has a crucial role in regulating cellular processes such as embryonic development, immune functions, necrosis, and apoptosis. The receptor for TNFα, Tumor Necrosis Factor Receptor 1 –(TNFR1) is ubiquitously expressed across almost all cell types. TNFα promotes survival and proliferation or induces apoptosis in a cell type-dependent manner. For instance, in human prostate carcinoma cells, TNFα induced apoptosis is dependent on P53 activation [62]. Also, TNFα treatment has been shown to increase nuclear and mitochondrial DNA damage in normal and cancer cells [63–65]. Interestingly, in UV-irradiated keratinocytes, TNFα treatment reduces DNA repair capacity [66]. These findings highlight a significant link between TNFα and DNA damage, which may influence DNA repair and subsequent cellular responses.

Visfatin: Adipokine visfatin is a cytokine with enzyme-like activities. It promotes glucose utilization and inflammatory responses by binding to insulin receptors at a site distinct from the insulin binding site. Elevated level of visfatin has been detected in breast and colon cancer patients [67,68]. The overall impact of visfatin on genomic stability appears to depend on cell type, duration of exposure, and the nature of DNA damage. Exposure of cells to visfatin for a short duration can lead to enhancement in NAD^+ biosynthesis, thereby supporting PARP1- and SIRT1-mediated DNA repair and promoting cell survival, under genotoxic stress. However, prolonged or high-level visfatin stimulation has been reported to induce persistent DNA damage and cellular senescence. Specifically, visfatin treatment has been shown to increase pH2AX expression and senescence-associated β-galactosidase activity in human dental pulp cells, indicative of DNA damage response (DDR) activation and growth arrest [69,70]. Moreover, under conditions of ionizing radiation, AMPK-dependent phosphorylation of NAMPT modulates NAD^+ homeostasis, balancing energy metabolism and DNA repair processes thereby facilitating cell survival [71]. Collectively, these findings suggest that the net effect of visfatin reflects a delicate balance between its pro-survival NAD^+-generating activity and its pro-damage oxidative signalling. This balance is influenced by the cell's metabolic state, duration of exposure, and DNA repair capacity of the specific cell type.

In summary, adipokines like TNFα and visfatin can alter DDR, leading to either increase in proliferation or induction of apoptosis in

cancer cells. These outcomes are influenced by the genetic status and cancer cell type, variation in the expression of the receptors as well as by extracellular environment together with the role of other adipokines and secretory factors.

Oxidative stress and inflammation

Oxidative stress and inflammation are central to the development of various diseases, including cancer. A study involving 83 obese individuals, 21 overweight, and 21 normal weight individuals reported a positive correlation between oxidative stress-induced DNA damage and BMI [72]. An article by *Kompella et al.*, highlighted the changes such as lipid toxicity, hypertrophy, and inflammation etc., associated with disruptions in the regulation of adipose tissue, which can trigger a cascade of molecular events. These alterations increase oxidative stress, promote DNA damage and genetic instability, thereby potentially contributing to cancer initiation and progression [42].

Additionally it has been shown that elevated levels of insulin, glucose, fatty acids, and inflammation in obesity contribute to the generation of ROS and lipid peroxidation products [28]. Also, hypercholesterolemia, for instance, has been linked to increase in ROS levels and pH2AX protein expression [73]. In Zucker rats (obese phenotype), oxidative stress-induced DNA damage in the liver has been correlated with higher steatosis scores compared to lean controls [74]. Moreover, a specific region on chromosome 15, known as a hotspot for oxidative stress-induced DNA damage, has been implicated in cancer etiology [75]. Interestingly, in prostate cancer cells cultured in serum from diet-induced obese mice, increase in, ROS production, double-stranded DNA breaks, and a shift towards aerobic glycolysis have been reported [76].

Obesity-induced inflammation contributes to tumor initiation and progression by enhancing DNA damage, leading to mutations in the *P53* gene and dysregulation of NFκB signalling [77]. Moreover, the normal functionality of immune cells particularly, the macrophages, is affected by inflammation and oxidative stress under obese conditions. Also, obesity-influenced macrophages can promote tumor progression and metastasis, derail the immune system, and reduce the effectiveness of cancer therapy [2]. These studies collectively underscore the significance of a relationship between obesity-influenced oxidative stress and inflammation with cancer.

Gut microbiota

The human gut harbours trillions of microbes and their composition is influenced by the host's niche, genetics, and diet [78]. Diet-induced and genetic obesity are reported to alter gut microbiota, leading to the accumulation of active bacterial metabolite DCA, a known DNA-damaging agent [79]. Elevated levels of DCA promote genotoxicity by increasing ROS production [80]. In hepatic stellate cells, DCA causes DNA damage and cellular senescence, resulting in the production of inflammatory cytokines creating a carcinogenic environment in the liver [79].

Dietary factors and nutrition

Macronutrients are essential for various aspects of genome maintenance, including nucleotide synthesis and replication (magnesium, zinc, iron, folate, and vitamin B12), DNA damage and repair (zinc, magnesium, iron, and niacin), methylation, chromosome stability (Vitamin B12 and folate), and prevention of oxidation of DNA (vitamin A, C, E). A comprehensive review of eight interventional studies in humans emphasized that food composition significantly influences DNA repair processes [81]. It is reported that a high-calorie or high-fat diet promotes DNA damage, while adequate intake of vitamins A, E, and C reduces it [82].

Vitamin E is known for its antioxidant properties and is linked with the expression of DNA repair genes. It prevents oxidative stress caused by hydrogen peroxide (H_2O_2) and increases the expression of DNA Methyltransferase 1 (*DNMT1*) and Mutator L Homolog 1 (*MLH1*), which are involved in epigenetic regulation and DNA repair [83]. Furthermore, it has been suggested that a diet deficient in protein but rich in calories can cause obesity and promote DNA damage, underscoring the importance of proper macronutrient intake in maintaining genome integrity [84]. With lifestyle changes, and imbalanced eating habits, studies on dietary factors that alter DDR are crucial, as they are likely to have an impact on the fate of cells.

Relevance of caloric restriction, anti-obesity drugs and intermittent fasting in DDR

Numerous studies suggest that interventions such as Caloric Restriction (CR), anti-obesity drugs, and Intermittent Fasting (IF) which offer benefits to individuals with obesity, also have implications in cancer therapy. For example, a study involving PBMCs from 82 cryopreserved samples of 41 patients before and after bariatric surgery indicated a reduction in DNA damage post-surgery [85]. In another related study weight loss following bariatric surgery in morbidity obese patients causes a reduction in DNA damage and normalization in the levels of oxidized glutathione as well as lipid peroxidation products [86].

In obesity, CR causes reduction in body weight and modulates expression of genes involved in hepatic stress and DNA damage. CR also diminishes mammary tumor growth in mice [87]. Additionally, a study on Zucker rats subjected to Roux-en-Y Gastric Bypass Surgery (RYGB) indicated a decrease in the levels of oxidative and nitrative stress markers in urine samples compared to sham operated rats. Interestingly, in sham-operated rats increase in DNA double-strand breaks in colon and kidney tissues were detected compared to those subjected to RYGB [88]. These studies indicate that reducing obesity can lower DNA damage, potentially restricting the transformation of normal cells into cancerous ones.

Among anti-obesity drugs, orlistat, a fatty acid synthase inhibitor, is reported to down-regulate the expression of a DNA repair enzyme, O6-Methylguanine-DNA Methyltransferase (MGMT) [89]. Also, in obese mice isografted with melanoma tumor, orlistat treatment combined with CR potentiates the efficacy of chemotherapy[90]. Another key target in obesity is the Glucagon-Like Peptide-1 Receptor (GLP-1R). Ligand for this receptor, GLP1 potentiates secretion of insulin, delays gastric emptying and promotes satiety [91]. GLP-1R is present in various organs/tissues like the nerves, islets, heart, lungs, and skin. A class of drugs termed GLP-1R agonists target hormone (Glucagon-Like Peptide-1) action [92]. GLP-1R agonists, such as liraglutide and the next-generation drug semaglutide, are FDA-approved and prescribed for weight management [92,93]. Semaglutide has enhanced efficacy and pharmacokinetic properties, therefore is effective at lower dosage [93–95]. In a study led by *Lindsey Wang et al.*, involving 1.6 million patients with Type 2 diabetes, semaglutide was found to significantly reduce the risk of obesity-related cancers. This study compared the outcomes among groups of patients treated with GLP-1R agonists, insulin, or metformin. The results indicated that in comparison to group of patients on insulin, notably GLP-1R agonists administered group of patients had lower risk of developing ten types of obesity-related cancers, including gallbladder cancer, meningioma, pancreatic cancer, hepatocellular carcinoma, ovarian cancer, and colorectal cancer [96].

Intermittent fasting (IF) and periodic fasting have also been shown to enhance the effectiveness of chemotherapeutic drugs in tumor-bearing mouse models [97]. In a heterozygous *P53*$^{+/-}$ gene mouse model, IF of one day per week prolonged survival significantly compared to an ad libitum diet [98]. Also, recently, a study involving 14 healthy human subjects, who intermittently fasted from dawn to sunset for >14 h, a serum proteome analysis revealed a signature indicative of protective signalling against cancer, metabolic disease, and neurological disorders

[99]. At the cellular level, IF regulates cellular stress response, enhances DNA repair, promotes mitochondrial energetics and induces autophagy leading to functional improvements in conditions such as cardiovascular disease, diabetes, and cancer [100]. Also, IF influences tumor progression as well as the efficacy of chemotherapeutic drugs [97].

Overall, weight loss interventions such as CR, anti-obesity medication, and IF have a positive impact on the DNA damage response, cellular metabolism, and immune response. Further investigation on the intricate relationship between anti-obesity interventions and DDR will be useful in elucidating the underlying mechanisms.

Pharmacological and clinical perspective

Genomic instability and defects in DNA damage response (DDR) including increased replication stress are critical drivers of cancer development. Interestingly, drugs that target DNA damage response (DDR) pathways have been shown to reduce the risk of obesity-related cancers. Specifically, metabolic regulators like metformin and resveratrol can positively influence DDR function by lowering oxidative stress, activating AMPK, and stabilizing P53, thereby contributing to the maintenance of genome stability [101–103]. Similarly, NAD^+ precursors such as nicotinamide riboside and nicotinamide mononucleotide support DNA repair through SIRT1 and PARP1, helping cells cope more effectively during metabolic stress [104].

Clinically, PARP inhibitors (e.g., olaparib) and ATR/CHK1 inhibitors (e.g., ceralasertib, prexasertib) drugs, which also affect DDR, are being evaluated in tumors characterized by metabolic dysregulation and DNA repair defects (Olaparib in Obese BRCA-Mutant Breast Cancer, NCT04887818; ATR Inhibitor Ceralasertib in Solid Tumors, NCT03704467). The importance of drugs targeting DDR for cancer therapy is being comprehensively evaluated as is indicated by ongoing clinical trials (Details of trials are listed in supplementary information attached). Moreover, the combination of metabolic reprogramming with DDR inhibition can be promising approach to enhance therapeutic response and overcome chemo-resistance in obesity models [105,106]. Collectively, these findings underscore that integrating metabolic modulators with DDR-targeted therapies represents a clinically relevant approach for the improving outcomes in obesity-associated malignancies.

Conclusion and future directions

The prevalence of obesity has significantly increased all over the world. It is a metabolic disorder which is positively correlated with increased cancer incidences. In this review attempt has been made to highlight, obesity-induced alterations which contribute to the derailment of DNA damage response (DDR) thereby potentially affecting carcinogenesis. Cancer is characterized by uncontrolled cell proliferation, often arising from cells which accumulate genetic alterations and a compromised DDR response, exacerbated by metabolic adaptability. Recent research underscores the intricate link between DDR as well as cellular metabolism, with DDR proteins regulating crucial metabolic pathways, such as the tricarboxylic acid cycle, glycolysis, and pentose phosphate pathway. The deregulation of DDR may thus play a significant role in the transitions from cellular changes to systemic effects by influencing various signalling pathways, including metabolic ones [12].

In this comprehensive review, we have explored the contemporary understanding of how obesity impacts DDR in cancer. Specifically, attention has been paid to addressing the significance of obesity-associated factors such as adipokines, oxidative stress, inflammation, altered gut microbiota, dietary factors, and metabolic interventions towards the DDR functionality which potentially affects phenotype and fate of cells. Attempts have been made to highlight that obesity exacerbates genomic instability and impairs DNA repair mechanisms, thereby promoting pro-survival signalling, facilitating precancerous transformations, and driving the development of chemo-resistance in cancer cells.

At a clinical level, DDR targeting drugs are integral to cancer treatment strategies (e.g. PARP inhibitors like olaparib, rucaparib, niraparib; ATM inhibitors- AZD0156, KU-60,019, AZD1390 etc.). Given that obesity-related factors can interfere with DDR, it may impact the efficacy of these therapies, particularly in patients with co-morbid conditions.

In conclusion, this review highlights the role of obesity-associated factors in derailing DDR, and their influence on the development of cancer as well as drug responses. A deeper understanding of the interplay between obesity-altered DDR and cancer could pave the way for more effective and affordable therapeutic strategies.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work Dr. Bhavana Deshmukh used ChatGPT to link the sentences and make a clear meaning. After using this tool/service Dr. Bhavana Deshmukh reviewed and edited the content as needed and takes full responsibility for the content of the publication.

CRediT authorship contribution statement

Bhavana Deshmukh: Writing – review & editing, Conceptualization. **Amrendra Kumar Ajay:** Writing – review & editing. **Manoj Kumar Bhat:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2025.102657. Clinical trial records were retrieved from the www.clinicaltrials.gov database during the period 2020–2022.

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