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Mitotic syndicates Aurora Kinase B (AURKB) and mitotic arrest deficient 2 like 2 (MAD2L2) in cohorts of DNA damage response (DDR) and tumorigenesis

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ABSTRACT

Aurora Kinase B (AURKB) and Mitotic Arrest Deficient 2 Like 2 (MAD2L2) are emerging anticancer therapeutic targets. AURKB and MAD2L2 are the least well studied members of their protein families, compared to AURKA and MAD2L1. Both AURKB and MAD2L2 play a critical role in mitosis, cell cycle checkpoint, DNA damage response (DDR) and normal physiological processes. However, the oncogenic roles of AURKB and MAD2L2 in tumorigenesis and genomic instability have also been reported. DDR acts as an arbitrator for cell fate by either repairing the damage or directing the cell to self-destruction. While there is strong evidence of interphase DDR, evidence of mitotic DDR is just emerging and remains largely unelucidated. To date, inhibitors of the DDR components show effective anti-cancer roles. Contrarily, long-term resistance towards drugs that target only one DDR target is becoming a challenge. Targeting interactions between protein-protein or protein-DNA holds prominent therapeutic potential. Both AURKB and MAD2L2 play critical roles in the success of mitosis and their emerging roles in mitotic DDR cannot be ignored. Small molecule inhibitors for AURKB are in clinical trials. A few lead compounds towards MAD2L2 inhibition have been discovered. Targeting mitotic DDR components and their interaction is emerging as a potent next generation anti-cancer therapeutic target. This can be done by developing small molecule inhibitors for AURKB and MAD2L2, thereby targeting DDR components as anti-cancer therapeutic targets and/or targeting mitotic DDR. This review focuses on AURKB and MAD2L2 prospective synergy to deregulate the p53 DDR pathway and promote favourable conditions for uncontrolled cell proliferation.

Contents

Abbreviations: ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia mutated and Rad3 related; ATRIP, ATR complexed with ATR-interacting protein; AURK, aurora kinases; AURKB, Aurora kinase B; BER, base excision repair; CDC25B, cell-division-cycle 25B; CDKIs, CDK inhibitors; CDKs, cyclin/cyclin dependent kinase; CPC, chromosomal passenger complex; DDR, DNA damage response; DSB, double strand breaks; HR, homologous recombination; ICL, inter-strand crosslink; MAD2L2, Mitotic Arrest Deficient 2 Like 2; MCC, Mitotic checkpoint complex; MCM, mini-chromosome maintenance; MGMT, Methylguanine-DNA Methyltransferase; MMR, mismatch repair; MNNG, Methylnitronitrosoguanidine; MRN, Mre11–Rad50–Nbs1; NER, nucleotide excision repair; NHEJ, non-homologous end joining; P53, protein 53; PARP1, Poly (ADP-ribose) polymerase 1; RPA, replication protein A; SAC, Spindle Assembly Checkpoint; TLS, translesion synthesis polymerases; TPX2, Targeting Protein for Xklp2.

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1. Introduction

Aurora kinases are members of a highly conserved family of serine/ threonine kinases. Mammals possess three Aurora kinase genes namely, AURKA, AURKB and AURKC [1]. These three proteins show a high degree of sequence identity, with 70 % homology in the catalytic domain, and have a similar 3D structure. Despite this, these proteins have distinct functions during mitosis and differ in their cellular localization. AURKB is a component of the chromosomal passenger complex (CPC). It interacts with the inner centromere protein (INCENP) as well as with the proteins survivin and borealin. It serves an essential role in chromosome segregation and cytokinesis. Furthermore, AURKB localizes at various regions of the centromere at different stages of cell division. These include prophase and metaphase centromeres, the cortex and spindle mid-zone in anaphase and the mid-body in telophase [2]. AURKC has a similar localization to AURKB but is only found in mammals and is only expressed in germ cells [3]. AURKA is required for a cell's entry into mitosis through the phosphorylation and activation of cell-division-cycle 25B (CDC25B), as well as centrosome maturation and spindle formation. AURKB and MAD2L2 are important mitotic proteins. The protein encoded by the *mad2l2* gene, also known as REV7, is a protein of 211 amino acids and plays a part in the prevention of the onset of anaphase in order to ensure the correct alignment of all chromosomes at the metaphase plate [4]. Other important processes where MAD2L2 plays a vital role include translesion DNA synthesis, mitotic control, and in the choice of repair pathway in DNA double-strand breaks. DNA polymerase zeta (ζ) is a key enzyme involved in the replication of damaged DNA by translesion synthesis. This enzyme is made up of many subunits, one of these being REV7. REV7 mediates the interaction between the catalytic subunit of DNA polymerase ζ, REV3L, and its DNA repair unit, REV1 [5].

Mitosis is a tightly regulated process by complexes of signaling pathways [6]. The mitotic chromatin architecture is distinct from the interphase chromatin arrangement. The spatial configuration of chromatin is important in ensuring that cells can fulfil their fundamental functions, from gene expression to specialised cellular division. The chromatin structure is affected by the status of the cell cycle and influences cell fate decisions through DNA-based activities such as DDR [7]. While there is a lot of evidence of DDR in interphase, evidence is emerging for a mitotic DDR, although this evidence remains largely unelucidated. Being considered the guardian of the genome, the interaction between p53-AURKB, a feedback loop, is important in cell biology. Several studies have reported the co-activity of AURKB and MAD2L2 in cancer cells. However, there is a lack of mechanistic studies to reveal the synergistic role AURKB and MAD2L2 in cancer biology and how this potential interaction may possibly deregulate the p53 signaling pathway. Both AURKB and MAD2L2 play a critical role in mitosis, cell cycle checkpoint and normal physiology. Contrarily, the aberrant expression of both these molecules has been reported in various cancers. Thus, this review will focus on how the prospective synergy between AURKB and MAD2L2 has the ability to deregulate the p53 DDR pathway and promote favourable conditions for uncontrolled cell proliferation. It will also explore the use of small molecule inhibitors of AURKB and MAD2L2 as anti-cancer drugs. Finally, it will focus on the targeting of the DDR components as anti-cancer therapeutic targets and detail the evidence for mitotic DDR.

2. AURKB and MAD2L2

Compared to AURKA, AURKB is the least studied member of the aurora kinase family. Aurora kinases are activated by autophosphorylation of the T-loop., being promoted by co-factors promote this autophosphorylation of Aurora kinases. Such co-factors include the microtubule-associated protein Targeting Protein for Xklp2 (TPX2) for Aurora A and INCENP for Aurora B [8]. In addition, AURKs interact with p53. In particular, p53 is phosphorylated at serine 269 and threonine 284 by AURKB, resulting in the inhibition of the transactivation activity of p53 [9]. Furthermore, the degradation of p53 is through polyubiquitination-mediated proteasome pathway. This is driven by phosphorylation of p53 at serine 183, threonine 211, and serine 215 [10–12]. Additionally, inhibition of the p53 protein family mediated tumor suppressor pathways takes place following the abnormal expression of Aurora kinases [1]. TP53 inhibits AURKA by binding to its promoter or by the transactivation of the p53 downstream targets such as p21, GADD45A and FBXW7a [13]. Inhibitors of AURKA and AURKB have been shown to induce cell death [14]. A reduced AURKB catalytic activity is necessary for abscission in normally segregating cells [15–17]. AURKB in particular, have become an important promising anti-cancer therapeutic target. Considering the normal physiological role AURKB plays in normal cells, targeting AURKB in cancer cells may be challenging, and thus more research still needs to be done to overcome the dual functional roles of AURKB due to its oncogenic roles and role in normal cells [18]. Mechanisms by

which p53 inhibits AURKB remain to be fully elucidated. However, a feedback regulatory loop between AURKB and p53 has been reported, Fig. 1.

Similarly to AURKB, MAD2L2 is the least studied member of the family when compared to MAD2L1. MAD2L2 is a chromatin binding protein involved in cell cycle regulation and DDR [19–22]. Previously, MAD2L2 was described as an accessory, non-catalytic subunit of DNA pol zeta (ζ), and its knockdown demonstrated hypersensitivity towards DNA damage [23,24]. Individual roles for AURKB and MAD2L2 in cell cycle regulation have been established. However, as mitotic proteins, the precise roles of AURKB and MAD2L2 in DDR remain to be elucidated. The synergistic oncogenic role of AURKB and MAD2L2 in mitotic DDR remain quite unclear. While the ataxia telangiectasia-mutated (ATM) pathway is the main detector of DNA damage and therefore DDR and acts upstream of the p53 pathway, the role of AURKB and MAD2L2 in the p53 pathway remains poorly understood. Although much work still needs to be done to elucidate the mechanisms of mitotic DDR, chromatin organization certainly plays a vital role in DDR.

3. Chromatin's role in cellular processes

For any cell to fulfil its functional duties such as gene expression and specialised cellular division, the special configuration of chromatin plays an important role. During the cell cycle, chromatin and nuclear envelope undergo assembly and disassembly. Chromatin modification and chromatin binding proteins influence the expression of key cell cycle, DNA repair, DNA replication and cell fate regulators [25]. Furthermore, the transcriptional and post-transcriptional regulation of histone biogenesis and modification are controlled in a cell cycle dependent manner. During different phases of the cell cycle, the chromatin architecture is dynamic to allow for DNA-based processes [7]. Hence, chromatin compacting may be influenced by the cell cycle status and thus influence cell fate decisions. During interphase, chromatin is loosely packed while mitotic chromatin is densely packed. During mitosis, chromatin condenses, and is difficult to access. Post-mitosis, chromatin decondenses, and is thus easily accessible. Two major events characterise mitotic exit, these being the reformation of the nuclear envelope protecting the segregated genomic material, and the establishment of the functional interphase chromatin within the reformed nuclear envelope [7]. Here the rod-shaped chromatids rapidly decondense into loosely organized, non-random structures that enable DNA-based processes to occur, Fig. 2. Notably, the removal of AURKB by p97 is important for chromosome unpacking and nuclear envelope reformation for the next cell cycle entry [26]. It has also been reported that heterochromatin unfolds in response to DDR [27].

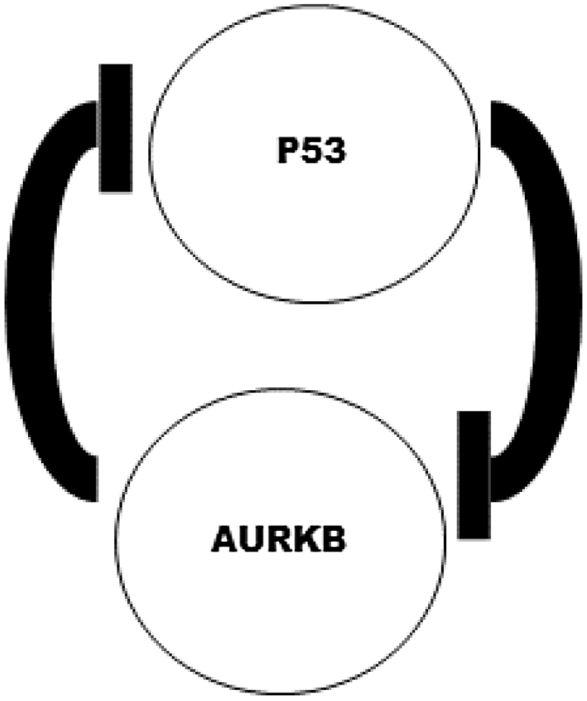

Fig. 1. A regulatory feedback loop between AURKB and p53. AURKB phosphorylates and inhibits p53. P53 in turn inhibits AURKB activity, during repair mechanisms.

4. DNA damage response (DDR)

4.1. Cell cycle and checkpoints

The proper replication of DNA and accurate chromosomal transmission to daughter cells is important for inheritance of an accurate and stable genome [28]. This replication and transmission of genetic material is achieved through the cell cycle. The cell cycle can be described as the series of events in which cells undergo growth and division by doubling cellular components and then accurately segregating into daughter cells [29]. This is achieved by stages namely, Gap phase (G1), DNA synthesis phase (S-phase), Gap phase 2 (G2) and the Mitotic phase. As they separate the S-phase and the Mitotic phase, the gap phases are delicate stages where cells grow, integrate growth signals and prepare for chromosome segregation [20,29]. The cyclin/cyclin dependent kinase (CDKs) complexes are the main drivers of the cell cycle. When CDKs are not bound to cyclins, they are inactive. CDK inhibitors (CDKIs) are negative regulators of the cell cycle by inhibiting CDK activity.

Living organisms themselves generate reactive agents posing a potential threat to genomic DNA. That is, a number of endogenous and exogenous DNA damaging agents constantly stress the eukaryotic genome. To maintain genomic integrity, cells respond by activating the DDR and DNA repair mechanisms [30,31]. The DDR can be described as an assembly of mechanisms that sense DNA damage, signal its presence and promote subsequent repair measures [32,33]. Upon activation, DDR allows sufficient time for DNA repair pathways to remove the damage in a specified substrate-dependent manner. These DNA repair pathways may include homologous recombination (HR), non-homologous end joining (NHEJ), base excision repair (BER), nucleotide excision repair (NER) and mismatch repair (MMR). Additionally, inter-strand crosslink (ICL) repair can also be employed to remove a few specific lesions. These DNA repair pathways are reviewed in detail by [28]. Two different pathways are used to repair double strand DNA breaks (DSBs). One of these is the HR pathway, which consists of a set of related sub-pathways. These pathways use DNA strand invasion and template-directed DNA repair synthesis to carry out high-fidelity repair [34,35]. NHEJ is the second pathway that organisms have evolved to resolve DSBs. Proteins involved in NHEJ pathway do not require DNA sequence homology but instead ligate broken DNA ends together. BER is the process used to repair single base damage that may not have a significant effect on the structure of the DNA double helix. BER occurs during the G1 phase of the cell cycle [36]. Bulky DNA lesions are normally repaired through NER. In order to initiate NER chromatin remodeling must occur in order to make way for the NER machinery at the point of the DNA lesion. Chromatin remodeling is also assisted by chromatin and NER components/ [37]. DNA replication can result in base mismatches. The MMR pathway is an evolutionarily conserved, pathway that functions to repair base mismatches' following DNA replication [38–43]. MMR functions to exchange mis-paired nucleotides and

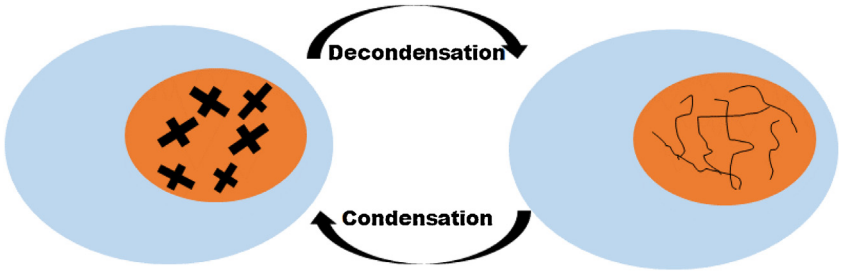

Fig. 2. Depiction of changes in chromatin structure during cell cycle transition from mitosis to interphase. At the onset of mitosis, chromatin is condensed into rod-shaped chromatids, while a rapid decondensation of chromatids into loosely arranged non-random structures occurs at mitotic exit.

direct damage repair. ICL repairs lesions where two bases from complementary strands are covalently linked due to damage to the DNA. This covalent bond may be due to crosslinking agents such as platinum compounds [44].

The results of DNA damage not being repaired include chromosomal changes, gene mutations, excessive cell death or the development of tumours. DDR pathways are activated as a result of genotoxic stress, [28]. During DDR, DNA damage/lesions are detected. This detection leads to the activation of a signal cascade, ultimately resulting in the repair of DNA, tolerance of the damaged DNA by the cell or even programmed cell death. This process is essential to maintain genomic stability following genomic insult, Fig. 3. Most of the DDR studies refer to DDR in interphase, while little is known about mitotic DDR.

4.2. DNA repair and tolerance

DNA replication and repair is facilitated by a family of DNA polymerases (pol). DNA polymerase families can be divided into A, B, C, D, X, Y, reverse transcriptase (RT) and primase and polymerase (PrimPol). Most family members of the A to D families are high fidelity polymerases involved in DNA replication and are associated with 3′ to 5′ exonuclease proofreading activity [45]. These include the highly accurate DNA polymerases δ (delta), ε (epsilon), α (alpha), and the error-prone translesion synthesis polymerases (TLS) Pol (zeta) ζ [4,46]. TLS polymerases in the B family lack the 3′ to 5′ proofreading exonuclease activity, such as TLS Pol (zeta) ζ [46]. The human TLS Pol ζ and its yeast homologue are heterodimeric proteins [4,47]. Additionally, the Y family are specialized TLS

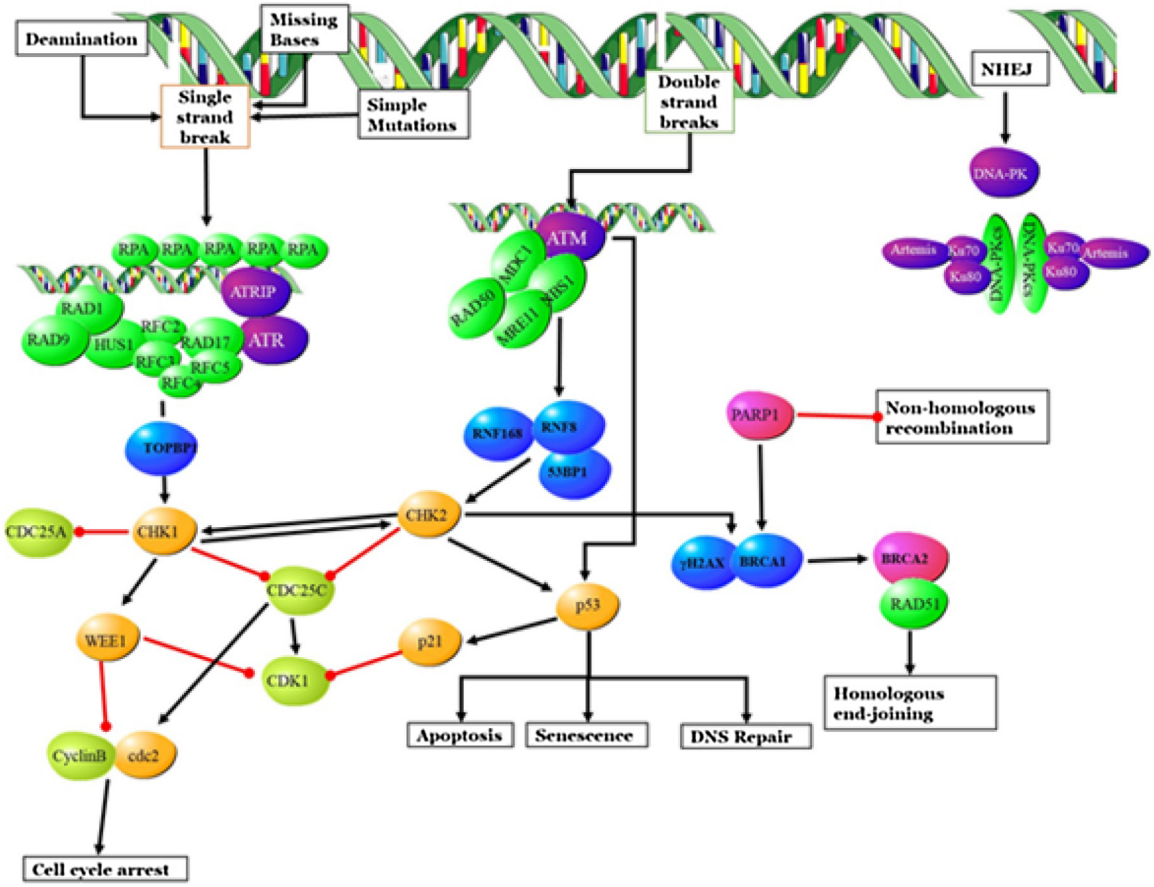

Fig. 3. DDR is the arbitrator between cell viability and cell death. The DDR pathway acts as an agent to maintain genomic stability by attempting to repair genomic DNA that is continuously facing insults. Depending on the severity of the damage, the cell can either be directed to repair, senescence or self-destruct.

polymerases. Furthermore, the error rates of replication polymerases are generally lower ($\sim10^{-6}$ and 10^{-8}) than the TLS polymerases with error rates of $\sim10^{-1}$ and 10^{-3} [45,48]. The replication of DNA is accomplished through the actions of high-fidelity error-free DNA polymerases. These polymerases cannot copy DNA when the parent strand is damaged [49]. To avoid replication fork breakdown, chromosomal instability and excessive cell death, special polymerases are required. These DNA polymerases are error-prone and are named the translesion synthesis polymerases (TLS polymerases). These polymerases are able to copy DNA across regions of damaged DNA [45,50,51]. In the 1970s, the first eukaryotic genes encoding error prone TLS polymerases were discovered, reversionless 1 and 3 (REV 1 and REV 3), and later on REV 7 was discovered. Understanding the potentially mutagenic TLS polymerases is key to a complete knowledge of cellular response to stress, cell death following DNA damage, induction of mutations, tumorigenesis and overall genomic stability [45]. The DNA pol family plays an important role in DNA replication and DNA repair.

In response to DNA damage initiated by genotoxic stress (endogenous or exogenous), DNA damage sensors must first detect the damaged DNA. Once these lesions are detected, then DDR is initiated. The. Mre11–Rad50–Nbs1 (MRN) complex detects DNA damage and acts to recruit members of the DNA damage response pathway and maintain genomic stability by processing DNA ends [31,52,53]. In particular, Rad50 recognizes the damaged DNA, other proteins required for DNA repair are recruited by Nbs1 to double strand breaks (DSB) lesions, and the nuclease activity of Mre11 processes the DNA ends [31]. MRN then recruits either ATM or Ataxia telangiectasia mutated and Rad3 related (ATR). The choice of which proteins are recruited depends on where the damage is. ATM is activated in response to DSB and chromatin remodeling while ATR is activated in response to stalled replication forks [54–56]. This is followed by a signaling cascade that activates repair checkpoints and recruits the remaining members of the DNA repair complex. The ATM signaling pathway acts upstream of the p53 signaling pathway.

4.3. DNA damage response (DDR) pathways

4.3.1. DDR: ATM pathway

Ataxia telangiectasia mutated (ATM) autophosphorylation is activated by the MRN complex. ATM auto-phosphorylation results in the dissociation of inactive ATM dimers into active monomers. The deregulation of the MRN complex results in the inhibition of the autophosphorylation of ATM preventing its recruitment to the dsDNA break site [57]. On the other hand, ATR is activated following blockage of DNA polymerases and the formation of lengthy ssDNA, which are formed by uncoupling of the mini-chromosome maintenance (MCM) helicase from the replication fork and then binding of replication protein A (RPA) to ssDNA [58]. RPA labelled ssDNA activates the recruitment of ATR complexed with ATR-interacting protein (ATRIP) and the Rad9, Hus1 and Rad1 (9–1–1) complex to the site of damage [59]. Furthermore, this 9−1-1 complex has also been shown to interact with other components of DDR such as p21. The activation of the G1/S cell cycle checkpoint requires the activity of ATM. Cells with damaged DNA are prevented from entering S-phase by this checkpoint. In addition to the role played by ATM in the G1/S checkpoint, ATM also plays a role in the activation of an intra-S-phase checkpoint. It has been demonstrated that cells deficient in ATM continue with DNA synthesis following induction of DSB, known as radio-resistant DNA synthesis phenotype [60]. Phosphorylation of checkpoint kinase 2 (CHEK2) by ATM reinforces its role during the intra-S-phase checkpoint. CHEK2 induces ubiquitinylation and degradation of the S-phase-promoting phosphatase CDC25A [56,60]. When active, this phosphatase promotes S-phase progression by activating cyclin-dependent kinase 2 (Cdk2), which is needed for DNA synthesis. ATM activation leads to p53 activation [56].

4.3.2. DDR: P53 pathway

The tumour suppressor protein p53, also known as the guardian of the genome plays a significant role in maintaining genomic stability. This is attributed to its ability to transcriptionally transactivate its downstream targets, which in turn prevents S-phase onset prior to facilitating DNA repair or eliminating cells with unrepairable DNA damage via apoptosis [56,61,62]. DNA replication stress resulting in double-strand DNA breaks DSBs activates P53. These DSBs are caused by ATM/ATR pathway responding to genotoxins and irradiation. The checkpoint kinases are activated with ATM phosphorylating the checkpoint kinase-2 (CHK2), following replication blockage and ATR phosphorylating CHK1. The activated checkpoint kinases activate p53 by phosphorylation [28]. ATM and ATR can also directly phosphorylate p53. Furthermore, ATM/ATR also phosphorylate the negative regulator

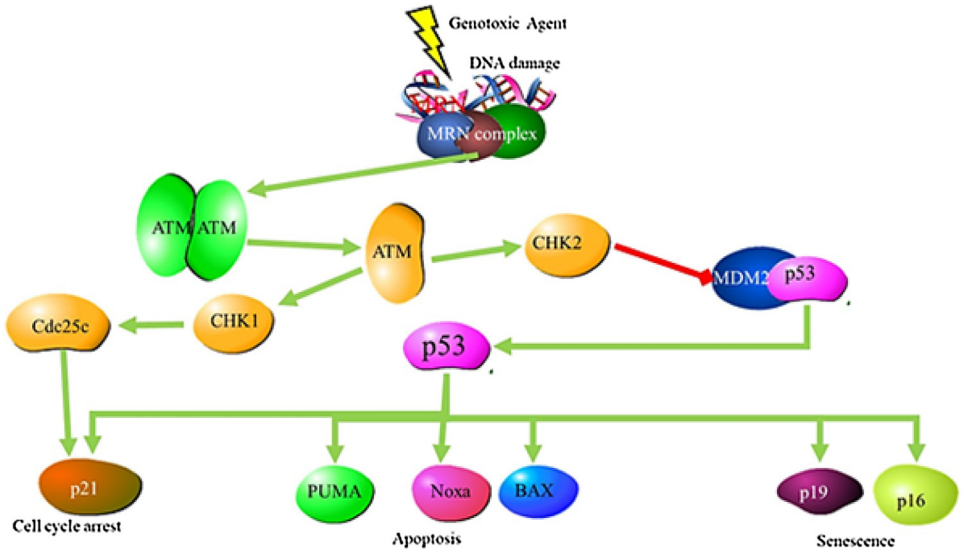

Fig. 4. The ATM and p53 DNA damage response pathway. Upon DNA damage, the MRN complex senses the lesions. This in turn activates the dissociation of inactive ATM, dimers to form an active ATM monomer. ATM then activates CHEK2. P53 can be activated by ATM directly or by CHEK2. P53 then transactivates its downstream targets.

of p53, MDM2. Following phosphorylation, MDM2 is degraded by ubiquitination, resulting in the stabilizing and activation of p53 [63,64]. The activated p53 then acts to upregulate the transcription of its downstream targets, such as p21 and p1, and suppress the expression of cyclin/CDK complexes. This in turn halts the cell cycle progression. P53 also represses the expression of pro-survival genes such as BCL-2 and Survivin. Failure to repair DNA damage during cell cycle arrest leads p53 to induce apoptosis [64]. As a result, pro-apoptotic genes such as BAX, BID and PUMA are activated, Fig. 4. Increasing evidence suggests the dysregulation of the p53 pathway in mitotic errors [12].

4.4. DDR in interphase vs mitosis

The primary mandate of DDR is to delay cell division until the repair of the damaged DNA is complete. Upon DNA damage, CHEK1 and CHEK2 deregulate PLK1, thereby delaying the onset of interphase and inhibiting entry into the mitotic phase. For this checkpoint to be removed, AURKA must activate the repressed PLK1 [65,66]. This checkpoint affords cells sufficient time to repair the damaged DNA prior to chromosomal segregation and cell division. However, cancer cells can bypass this checkpoint, with persistent DNA damage, and chromosomal mis-segregation [67]. Cells undergoing the transition from G to M phase, have the ability to inhibit the DDR, allowing them to continue through the cell cycle [6,66,68]. Following DNA double strand breaks, the normal DDR involves the activation of the ataxia telangiectasia mutated (ATM) and the DNA-dependent protein kinase (DNA-PK), protein kinases. This is followed by the recruitment of multiple proteins and protein complexes to the sites of DNA damage. These include the histone H2AX phosphorylation together with recruitment of mediator of DNA damage checkpoint 1 (MDC1), and the Mre11–Rad50–Nbs1 (MRN) complex. The recruitment of these proteins result in multiple detectable downstream responses to DNA damage [69,70]. These downstream responses include the recruitment of Ring Finger Protein 8 (RNF8) by MDC1, leading to increased RNF168 activity. These RNF proteins ubiquinate the H2AX histones [69,71]. This process of ubiquitination leads to chromatin changes. In turn, p53-binding protein 1 (53BP1) and Breast Cancer gene 1 (BRCA1) are recruited for NHEJ and HR [70,72]. It was the absence of these downstream responses in mitotic cells, following exposure to DNA damaging agents that led to the conclusion that DDR was curtailed in these cells [69,70]. During mitosis, CDK1 phosphorylates and inhibits RNF8 [73]. Furthermore, CDK1 inactivates 53BP1. As a result, NHEJ is inhibited. Additional phosphorylation of 53BP1 by Polo Like Kinase 1 (PLK1) leads to CHEK2 phosphorylation, thus preventing DDR [71].

Since minimal DNA repair processes occur during mitosis, the majority of the repair processes occur in the G1 phase. This was demonstrated by Terasawa et al. (2014). In this study, cells undergoing mitosis were treated with the topoisomerase II inhibitor, etoposide. This resulted in the accumulation of DSBs and dicentric chromosomes [71]. Despite this, cells undergoing mitosis are capable of repairing DNA damage. Gomez-Godinez et al., (2020) showed that cells undergoing mitosis initiate DNA repair through different mechanisms than those observed in cells in other phases. This different process is capable of repairing DNA when both ATM and DNA-PKs are inhibited but is induced when Poly (ADP-ribose) polymerase (PARP) is inhibited [74]. Despite this crosstalk between DDR and mitotic signaling being poorly understood, it still has high potential as a cancer therapeutic target [75]. The decrease in the efficiency of the DDR during mitosis can result in chromosomal rearrangements. It may also result in structural chromosomal rearrangements where only portions of the chromosome are duplicated or deleted [76]. A similar situation is observed in cancer cells where inhibition of the DDR leads to the accumulation of genetic damage [67]. Understanding DDR during the mitotic phase remains elusive, as it was previously thought that mitotic cells are not capable of DNA repair [77,78]. Emerging evidence reveals otherwise, with DDR during mitosis targeted for effective cancer therapy [74].

4.5. DDR significance and cell fate

In mammalian cells DDR includes Ataxia telangiectasia mutated (ATM), Ataxia telangiectasia mutated and Rad3 related (ATR) and Poly (ADP-ribose) polymerase 1 (PARP1). It also includes key transcription factors, which in turn target their downstream effectors such as BRCA1, NF-Kβ, AP-1 and p53. Interestingly, the induction of DNA repair genes in mammalian cells leads to comparatively lower expression of DNA repair proteins than in other organisms. This can be seen in the activation of Methylguanine-DNA Methyltransferase (MGMT). This activation leads to a 15-fold increased expression of this protein in rat liver, and approximately 5 fold increase in expression in human hepatoma cells *in vitro*. Despite these being comparatively high levels of increase in expression [30,79], it is small compared to the increase in DDR proteins in other organisms following DNA damage. For instance, in bacteria there is a 1000 fold increase in the expression of the DNA repair genes such as adenosine deaminase (ADA), following Methylnitronitrosoguanidine (MNNG) exposure. However, animal cells express DNA repair genes at a basal level that is detectable. An increase in the expression of these genes is biologically significant, as even a slight increase in expression may significantly improve DNA repair.

5. AURKB, Spindle Assembly Checkpoint (SAC) and chromosome segregation

Previous studies have shown that AURKB and MAD2L2 are frequently overexpressed in human tumours. This causes aberrations in spindle assembly checkpoint (SAC), leading to chromosomal mis-segregation and centrosome amplification. Which in turn results in chromosomal instability and tumorigenesis [80]. Aurora B forms part of the Chromosome Passenger Complex (CPC) and is partnered with Inner centromere protein (Incenp), Survivin and Borealin. Chromosomal bio-orientation prior to segregation is ensured by AURKB and other CPC components. AURKB destabilizes incorrectly attached microtubule (MT)–kinetochore connections via mitotic centromere associated kinesin (MCAK) [81,82]. The phosphorylations (by AURKB) are removed by protein-protein interactions (PPIs), once tension is established and the outer kinetochore is separated from the centromeric AURKB [83–85]. By generating unattached kinetochores during error correction, AURKB then effects the SAC by recruiting SAC components such as MAD2L2 to the kinetochore. SAC must be rapidly silenced following the correct and stable attachment of all chromosomes, to allow entry into anaphase and the exit from mitosis [86]. The silencing of SAC at the kinetochores is meditated by the release of cell division cycle 20 (CDC20), which degrades securin (important for anaphase onset), thereby detaching sister chromatids [87]. This is followed by anaphase-promoting complex/cyclosome (APC/C) activation, allowing the cell cycle to progress to anaphase [88–90]. The mitotic checkpoint complex (MCC) is the main component of SAC. MCC is the effector of the SAC and the main physiological function of the MCC is to inhibit APC. MCC has four types of protein components, BUBR1, BUB3, CDC20 and MAD2 [91]. All four proteins are evolutionarily conserved. Interestingly, other APC/C inhibitors such as Emil and Mitotic Checkpoint Factor 2 (MCF2) may exist. BUBR1 is the largest protein in the MCC, and is essential for MMC stability and APC/C inhibition. BUB3 forms a complex with BUBR1 and targets them to the kinetochore. CDC20 is

regarded as a key subunit of MCC and binds to and interacts with BUBR1 and MAD2. In the presence of the unattached kinetochores, MAD2 acts as a critical signal transducer of the SAC. As MAD2 can adapt to two different fold conformations, the O and C, its ability as SAC signal transducer depends on its conformational change from O to C. Interestingly, the majority of MAD2 during interphase exists in O confirmation. Details of O to C MAD2 conformation remain to be fully understood. It has been revealed that O-MAD2 does not bind other MCC components, and thus has been rendered inactive by checkpoint transition. The O to C MAD2 confirmation changes following nuclear envelope membrane break [92,93]. When sister chromatids are properly aligned and kinetochores properly attached to the spindle microtubules, cells can silence the MCC within 15 min for the onset of anaphase [94]. As kinetochores attach, they stop generating the checkpoint signals and only unattached kinetochores still transduce checkpoint signals. Cells still need to allow for sufficient time to disconnect the MCC:APC/C complexes. This disassembly requires energy input and proper regulation to permit effective transition to anaphase [95,96].

6. Communication between the Mitotic checkpoints, DDR and cell death

Emerging evidence indicates the communication between DDR and SAC and the role of DNA damage sensors ATM and ATR in SAC regulation [74]. For example, Kim and Burke (2008) showed that in yeast cells with DNA damage, the progresses to mitosis from interphase, induces SAC, and that SAC is dependent on the ATM and ATR yeast homologs, Mec1 and Tel [97]. Eliezer et al., (2014) demonstrated that DDR components ATM, H2AX, and MDC1 are required for kinetochore localization of the mitotic checkpoint complex (MCC) proteins MAD2L1 and CDC20 and for the MCC integrity [98]. Despite the emerging evidence of the communication between SAC and DDR, exact mechanisms remain to be comprehended [98–100]. Similarly, the mechanisms of SAC dysregulation and cell death are poorly understood. When cells encounter mitotic failure, they activate intrinsic oncosuppressive mechanism that senses this mitotic failure and are driven to anti-proliferative fate, senescence or apoptosis, a phenomenon known as mitotic catastrophe [101]. However, it is not properly understood which signaling pathways are involved in mitotic catastrophe. Thompson et al. (2019) reported that excessive DNA damage results in the increased expression of apoptotic machinery, as well as increased crosstalk between SAC and these apoptotic components [6]. SAC has also been reported to be involved in cells progressing to mitosis following mitotic catastrophe when cells were treated with DNA damaging agents [102].

7. MAD2L2 and DDR

Although implicated in DDR, the precise role of MAD2L2 in mitotic DDR remains to be understood. The catalytic subunit of Pol ζ, REV7, assists in the direction, sequential insertion and extension steps that take place during the repair of DNA lesions [4]. MAD2L2 is recruited to the site of DSB, shortly after DNA damage. However, MAD2L2 is not involved in the initiation of DNA repair. This differs from other molecules that are recruited to sites of DNA damage such as 53BP1 (p53 binding protein) which is recruited to DSB. This protein promotes non-homologous end joining (NHEJ). It also recruits RIF1 (telomere associated protein). RIF1 inhibits the resection of the ends of DNA [103]. It is predicted that MAD2L2 acts downstream of RIF1 preventing the resection of the 5′end of DNA. Furthermore, genomic instability is prevented through the proper repair of lesions in DNA as well as the inhibition of DNA repair at the sites of telomeres. Currently the mechanisms involved in telomere-driven genomic instabilities are unknown. Aberrant expression of MAD2L2 during DNA repair at uncapped telomeres and DSBs has been predicted to potentially contribute to genomic instability [104]. Furthermore, telomere fusion involving defects in capping requires MAD2L2.

8. Protein interaction networks

Protein interaction networks were determined by STRING and modelled by Cluspro. Fig. 5 shows a STRING interaction network of AURKB, MAD2L2 and p53. AURKB and MAD2L2 do not share similar interacting partners (Fig. 5A and B). A strong interaction between AURKB and p53 is evident, while a weak interaction is illustrated between AURKB and MAD2L2, and p53 and MAD2L2 (Fig. 5C and D). Fig. 6 shows protein interaction models by the Cluspro online tool.

8.1. STRING interaction network

Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database was used https://string-db.org/ to determine PPI or gene interaction networks. AURKB (NM_004217), MAD2L2 (NM_006341) and p53 (NM_000546) GenBank accession numbers were uploaded onto the STRING database, using the parameters of 'multiple proteins' and 'homo-sapiens' functions. The minimum required interaction score was set at 0.4, the medium confidence. The interaction network may be advantageous to represent information other than lists of genes or pathways, as it describes which genes are closely connected within a given pathway. Hence, it has the potential to detect more indirect signals, such as local disturbances within known pathways, as well as within pathways that may not yet have been described [105].

8.1.1. AURKB, MAD2L2 and P53 interaction

Evidence for the existing PPI between AURKB and p53 is depicted below by *in-silico* analyses, Fig. 5. Although proposed here, the established interaction between AURKB and MAD2L2 is yet to be determined. This *in-silico* analysis reveals a strong interaction between AURKB and p53. While not shown here, of the two isoforms AURKA and AURKB, the latter shows a weak interaction with MAD2L2, compared to no AURKA-MAD2L2 interaction occurring. Notably, p53 also shows a weak interaction with MAD2L2. The AURKB, MAD2L2 and p53 PPI warrants further investigations, and may elucidate in mitotic DDR events. Furthermore, the Cluspro online analysis tool was used to model AURKB, MAD2L2 and p53 protein structures, and then determine and predict PPIs. Fig. 6 represents the AURKB, MAD2L2 and p53 interactions as modelled by Cluspro.

8.2. Cluspro protein modelling and interaction

The Cluspro online analysis tool was used to create protein–protein interaction models [142–144]. The NMR structures for TP53 (PDB ID 3DCY) and MAD2L2 (PDB ID 5XPU) as well as the X-ray diffraction structure for AURKB (PDB ID 4AF3) were used in the analysis which returned various interaction models. Based on the energy scores the models selected for each interaction were as follows: for the interaction between p53 and MAD2L2, model cluster 1 was selected. This cluster contained 65 members and had an energy score of -838.5 for the central model and a score of -902.7 for the model with the lowest energy. For the interaction between p53 and AURKB, the selected cluster of models was cluster 2 containing 50 members with an energy score of -837.3 for the central model and a score of -945.2 for the lowest energy model. For the interaction between MAD2L2 and AURKB the selected cluster of models was cluster 1 containing 78 members and had an energy score of -1078 for the central model and a score of -1166.2

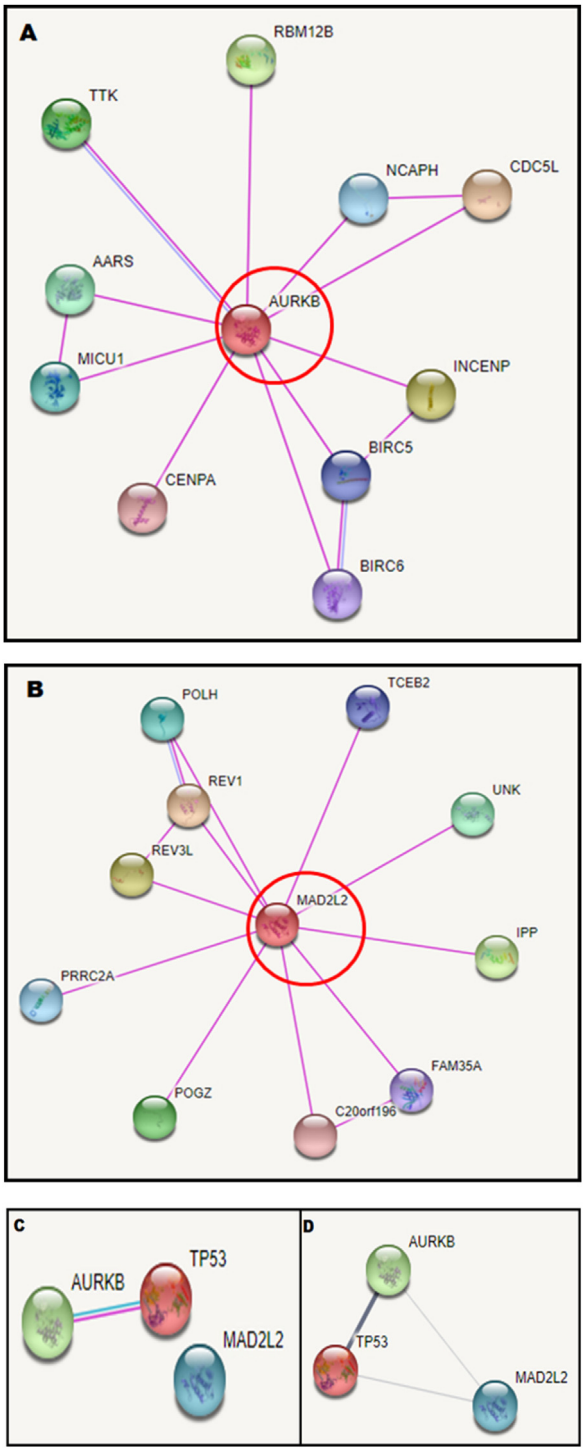

Fig. 5. STRING protein-protein interaction networks for AURKB, MAD2L2 and p53. A shows PPIs for AURKB, **B** illustrates PPIs for MAD2L2, **C** demonstrates an experimentally verified PPI between AURKB and p53, while **D** represents *in-silico* PPI for AURKB, MAD2L2 and p53. A to C represent experimentally confirmed PPIs.

for the model with the lowest energy. The PDB files of the selected models were used to generate 3D space filling models of the interaction using SWISS-PDB viewer [145].

9. DDR, anti-cancer therapies, and the future

The DDR pathway is known to play important roles in a variety of aspects that contribute to the development and progression of cancers [56]. This is shown by mutations in the BRCA1 and BRCA2 genes that play key functions in DDR. Women who carry a defective allele in one of these genes are at an increased risk of developing breast or ovarian cancer than their counterparts in the general population [106,107]. It has also been revealed that malignant tumors show deregulation of ATM and p53 proteins [56,108]. With the deregulation of the key DDR proteins, cells may proliferate uncontrollably, breaching the proliferation barrier set by the DDR and leading to genomic instability [11,109]. In addition, DDR mechanisms also affect cancer treatments that rely on their ability to induce DNA damage. These include treatments such as chemotherapy and radiotherapy. The damaging of DNA is extremely cytotoxic to proliferating cells such as cancer cells. Contrarily, cancer cells can self-activate DDR; thereby resist treatment [110,111]. Since chemotherapy and radiotherapy generally lack selectivity between normal and cancer cells, the cytotoxicity induced in normal cells and the associated side effects are limiting factors in this therapy. Furthermore, research has shown that the dysregulation of the DDR pathway can lead to the development of resistance to different types of genotoxic therapy [112–114]. DDR has thus become a target for cancer therapy, and key components may be used as radio-or-chemo sensitizers. Additionally, while not all the DDR components may be defective, targeting the proper functioning DDR components can be disadvantageous to the cancer cells exploiting this mechanism. This was first observed in the BRCA1 and BRCA2 genes, wherein cancer occurring due to mutations in these genes can be treated effectively using small molecule inhibitors of poly (ADP-ribose)-polymerase (PARP). As is well known, PARP is a DDR protein that detects and through base excision repair, repairs ssDNA breaks [56,115]. The PARP inhibitor, olaparib has been used for the treatment of BRCA1/2 mutated breast or ovarian cancer, and also for treating metastatic prostate cancer [33,116,117]. While interphase DDR interventions may be successful, mitotic DDR interventions should also be explored. Integrated and targeted DDR may be an effective strategy against cancer, Fig. 7.

9.1. DDR small molecule inhibitors

One of the major challenges of the development and use of small molecules in DDR is attempting to disturb macromolecular interactions, and not necessarily inhibiting one target [118]. For instance, recurrent ovarian cancer patients develop resistance against olaparib (PARP inhibitor), limiting the effectiveness of single small molecule inhibitor therapy [119–122]. A therapeutic area that remains largely to be explored is the development of effective and specific inhibitors that target protein-protein interactions (PPI) such as the inhibition of RAD51-BRCA2 protein interaction and protein-DNA interactions (PNI) such as RAD51 and RAD52 proteins binding ssDNA, in an attempt to perturb macromolecular interactions and to circumvent single molecule therapy resistance.

10. Targeted molecular therapy: small molecule inhibitors

The deubiquitinating enzyme DUB USP35 has been shown to regulate AURKB protein levels by binding to and deubiquinating AURKB. This interaction inhibits AURKB proteosomal degradation mediated by APC CDH1. Controlling the downstream signaling of AURKB, USP35 depletion leads to cytokinesis defects and other mitotic defects [123]. AURKB inhibitor barasertib and S49076 have been shown to decrease levels of phosphohistone H3 (pH3), a key product of AURKB. This resulted in G1/S phase arrest and polyploidy, followed by cell death in cancer cells. In non-small cell lung cancer (NSCLC), AURKB is a potential target, with its upregulated expression associated with anti-EGFR therapy

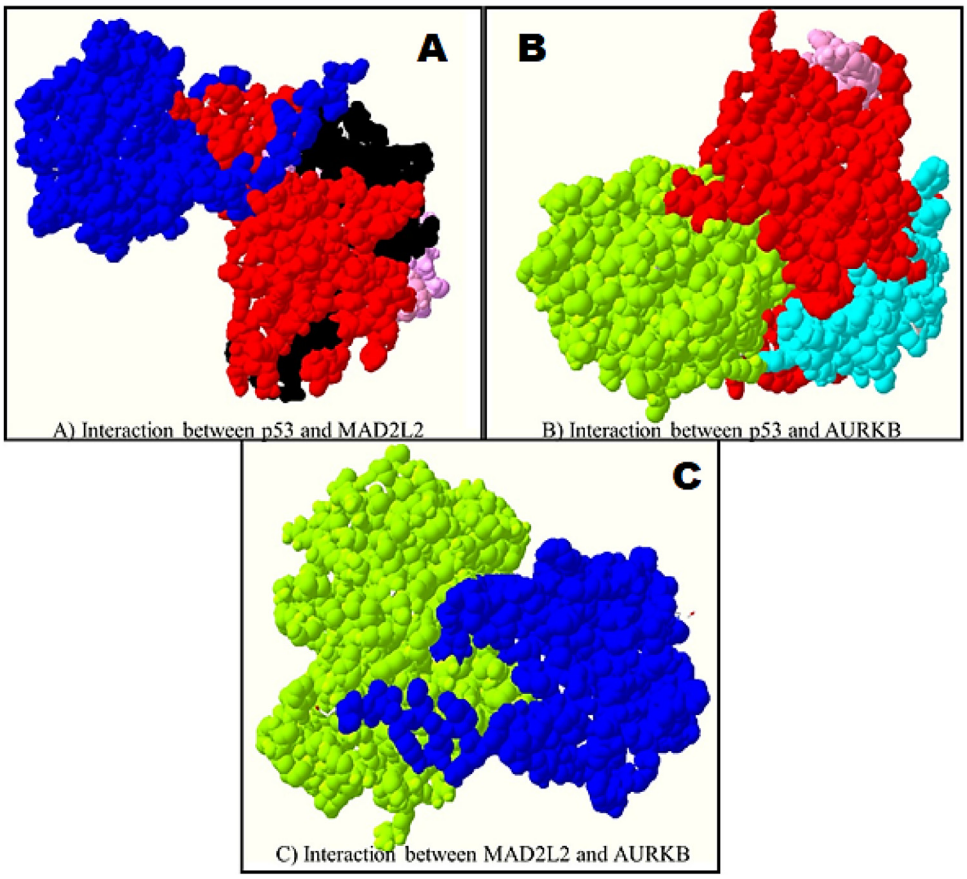

Fig. 6. Protein modelling and interaction by Cluspro. The figures are predicted interaction models generated using the Cluspro interaction server. These models predict the interactions between **A**) p53 and MAD2L2 (**B**) p53 and AURKB and (**C**) MAD2L2 and AURKB. The interaction models were created using existing X-ray crystallographic structures for all three proteins. MAD2L2 is coloured blue, while AURKB is colored green. The p53 protein is colored by domains. The amino-terminus domain residues 1-42 marked in dark blue; the acidic transactivation domain (residues 40-92) is shown in pink; the DNA binding domain (residues 101-306) is depicted in red and the oligomerization domain (residues 307-355) is represented in light blue.

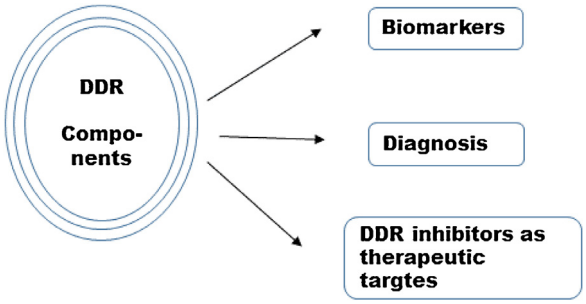

Fig. 7. DDR as a promising anti-cancer target. The DDR pathways and components are emerging as promising therapeutic targets in cancer treatment, but can also be used as diagnostic biomarkers in cancer patients.

resistance and decreased survival [124]. Upregulated AURKB expression drives the cell cycle and promotes the survival of cancer cells. Despite its yet to be established oncogenic role increased expression of AURKB has been implicated in various cancers [18]. Through its negative regulation of p53, AURKB downregulates the expression of p21, an important cell cycle regulator. In addition to this, AURKB suppresses BRCA functions. Furthermore, it has been shown that AURKB and its substrate histone deacetylases (HDACs) together promote the survival and proliferation of lymphoma by activating the AKT/mTOR signaling pathway [125]. Contrarily, AURKB inhibition by barasertib has been shown to induce both necrosis and apoptosis in metastatic melanoma [126]. Decreased AURKB in lymphoma cells allows the upregulation of CASP3, while downregulating cyclin B1 and cyclin D1. Aberrant expression of AURKB promotes survival while inhibiting apoptosis and cell death mechanisms. Additionally, AURKB forms a complex with novel inhibitor of histone acetyltransferase repressor (NIR) and p53. NIR works as a scaffold protein, mediating the interaction between AURKB and p53.

Li et al., (2019) showed that AURKB prevented aneuploidy in oxidatively damaged cells. This group showed that the AURKB inhibition caused mis-segregation of chromosomes, abnormal chromosome number, abnormal spindle structures and reduced MAD2L1 expression in IVF embryos. This group further suggested that AURKB responds to DDR by activating SAC via MADL1 and interacting with Histone H3 phosphorylated at serine 10 (H3S10 P) which is required for self-correction of aneuploids. Immunohistochemistry analysis also revealed the co-localized AURKB with MAD2L1 [127]. However, establishing the nature of the interaction between AURKB and MAD2L2 remains to be elucidated. AURKB also acts upstream of Chk1 during DDR [128]. Loss of AURKB causes SAC disfunction and chromosomal abnormalities during mitosis [18,129,130].

10.1. AURKB inhibitors

Both AURKA and AURKB have been shown to be overexpressed in various cancers including lung cancer and there have been advancements in the development of small molecule inhibitors against AURKA and AURKB [131,132]. Helfrich et al., (2016) also

showed that small cell lung cancer (SCLC) with upregulated c-Myc expression responds positively to AURKB inhibitors [133]. Treatment of human colon cancer cells with barasertib led to polyploidy (a hallmark of anti-tumour activity) after aberrant mitosis. This was coupled with Rb hypo-phosphorylation [134]. Akiyama et al., (2014) showed that cisplatin and oxaliplatin resistant cancer cells responded to the AURKB inhibitors barasertib and ZM447439 [135].

DDR is an important anti-cancer therapeutic target as when DDR unsuccessfully attempts to repair damaged DNA, then cancer cells die. Interestingly, most of the small molecules being developed and that have progressed to advanced clinical trials are the DDR kinase inhibitors. These include kinase inhibitors for ATM (Ataxia talangiectasia muated), ATR (ATM and Rad3 related), PLK1 (Polo- like kinase), DNAPK (DNA-dependent protein kinase), Wee1, CDKs (cyclin-dependent kinases), PI3K-AKT-MTOR, CHK1, CHK2 and AURKses. AKT inhibitors are also being evaluated in clinical trials [136–141].

10.2. MAD2L2 inhibitors

MAD2L2, plays an important role in various cellular pathways including cell cycle control, translesion DNA synthesis and NHEJ [142]. MAD2L2/REV7, together with 3 additional subunits RINN1, RINN2 and RINN3 form Shieldin. This is a quaternary complex that shields ssDNA ends and facilitates NHEJ by preventing BRCA1 dependent HR [104,143–146]. Shieldin functions as a downstream effector of p53 binding protein 1-Rap1-interacting factor 1 (53BP1-RIF1) [147]. Wang et al., (2019) showed that Ras Associated Nuclear protein (RAN), a small GTPase, potentially regulates REV7 upstream. In essential cellular processes such as nuclear transport, nuclear envelope formation and mitotic spindle assembly, RAN interacts with its binding proteins. RAN controls these cellular processes by switching between GTP form (RanGTP) and GDP form (RanGDP). Although the REV7/RAN PPI remains to be fully understood, MAD2L2/REV7 preferentially interacts with RanGTP. Shieldin and 53BP1-RIF1 may be key factors in decoding MAD2L2-AURKB-p53 network, particularly in the p53 deregulation by aberrant AURKB-MAD2L2 expression.

The development of MAD2L2/REV7 inhibitors is also a work in progress. Actis et al., (2016) discovered compound 7, a REV7 small molecule inhibitor which was shown to be a promising chemotherapeutic sensitizer [148]. Another group, Wojtaszek et al., (2019), demonstrated JH-RE-06, a small molecule inhibitor disrupting REV1/REV7 PPI, mediating mutagenic TLS, to sensitize tumour cells to cisplatin, reduce mutagenesis, suppressed tumour progression in mice and prolonged animal survival [149]. Ren et al., (2017) also emphasized that structural insights into REV7 inhibition hold promising therapeutic potential [150].

Marima et al., (2020a) demonstrated that AURKB was elevated in NSLC *in vitro* models. This was coupled by the overexpressed MAD2L2 gene. Interestingly, this study revealed the potential anti-proliferative effects of Efavirenz (EFV) in lung cancer cells, where treatment of cancer cells with EFV resulted in downregulated expression of both AURKB and MAD2L2, in concert with increased expression of cyclin dependent kinase inhibitors (CDKIs) [151]. Similarly, Marima et al., (2020b) showed upregulated p53 expression followed by decreased AURKB and MAD2L2 gene expression in lung cancer A549 adenocarcinoma cells treated with protease inhibitors [152]. Furthermore, Gene Ontology (GO) analysis revealed upregulated serine/threonine kinase activity in lung cancer cells, AURKB being a member of this protein kinase family [153]. Several other studies have implicated the aberrant expression of AURKB not only in lung cancer, but also in various cancer cells. The co-transcriptional regulation and co-cellular localisation of these two proteins would be interesting to pursue and further understanding in the underlying molecular mechanisms associated with their aberrant expression and tumorigenesis.

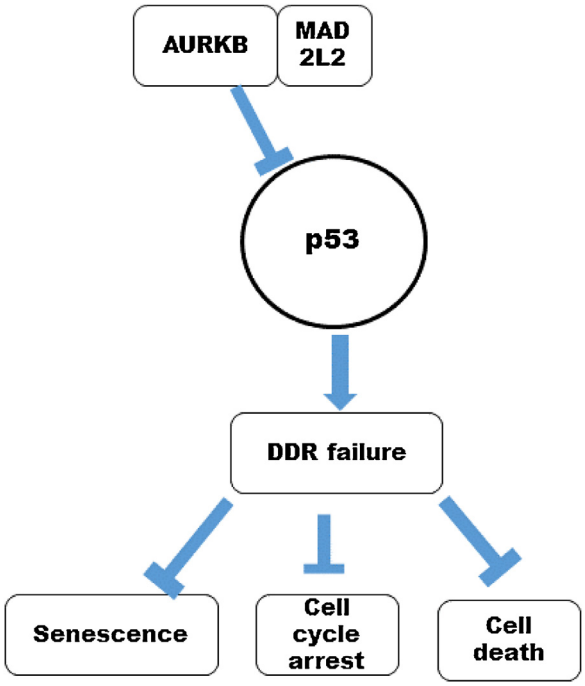

Fig. 8. AURKB and MAD2L2 work in synergy to dysregulate the p53 signaling pathway. This creates favorable conditions for uncontrolled cell proliferation and eventually leading to tumorigenesis.

11. Significance and implications

To date, the molecular events leading to dynamic interaction between highly condensed and loosely arranged chromatin remain to be fully elucidated. A deeper understanding of the key roles played by AURKB and MAD2L2 individually and as potential interactors, in their signalling pathways and targets may potentially contribute to closing the gap in our current understanding of the DDR in mitotic cells. Furthermore, key questions to this phenomenon still require answers. These include: what are the key role players in mitotic DDR vs interphase DDR. Changes in the expression and activity of these key players between normal cellular function and cells going through tumourigenesis, may aid in the identification of future drug targets. A major question still remains, as to how DNA damage is sensed and repaired during mitosis. While mitotic DDR remains poorly understood, these two poorly understood members of the AURK and MAD2 families are novel targets for the development of therapies targeting mitotic DDR. Here we propose that a better understanding of the AURKB-MAD2L2 AURKB-P53 and MAD2L2-P53 interactions will aid in the development of effective small molecule inhibitors either for these molecules or for their interactions. Targeting DDR components, particularly interphase DDR is rapidly emerging as future cancer therapy. However, the development of these future therapies requires an overall better understanding of mitotic DDR.

12. Conclusions

DDR components are now known to play vital roles in tumorigenesis, and are emerging as double-edged swords in promoting oncogenesis and normal cell function. When

appropriately regulated, DDR pathways control the delicate balance between cell death and proliferation by preventing excessive cell death or proliferation. This is profoundly associated with p53, the centerpiece of DDR. Components of the DDR play a significant role as cancer biomarkers, in cancer diagnosis and treatment. Mitotic DDR, previously assumed to be non-existent, is emerging as an important anti-cancer therapeutic target. Whilst individual DDR inhibitors have shown efficacy over the years, emerging research prompts the development of inhibitors that target DDR interactions, rather than single molecules. Furthermore, understanding the mitotic DDR will be of significance in cancer biology, since mutations that accumulated during mitosis can lead to chromosomal abnormalities, genomic instability, senescence and premature cell death [74]. It is therefore proposed here that as part of the chromosome passenger complex (CPC), AURKB overexpression affects the spindle assembly checkpoint (SAC) by recruiting its (SAC) components such as MAD2L2. The aberrant expression of AURKB and MAD2L2 deregulate the p53 pathway, creating favourable conditions for uncontrolled cell proliferation, leading to tumorigenesis, Fig. 8.

The overexpression of AURKB also augments the expression of MAD2L2, Fig. 6. In turn or perhaps simultaneously, p53 activity is inhibited by AURKB phosphorylation resulting in excessive cell proliferation. CPC components such AURKB and MAD2L2 (SAC component), and their oncogenic role in p53 deregulation, warrants further research and may significantly contribute to the elucidation of mitotic DDR, and its potential as an anti-cancer therapeutic target. DDR supports genome integrity in normal cells, while improper DDR regulation can render cancer cells radiation and chemotherapy resistance.

Author contributions

All authors wrote and reviewed the manuscript. All authors approved the manuscript.

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Declaration of Competing Interest

The authors report no declarations of interest.

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