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DNA damage response in nephrotoxic and ischemic kidney injury

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Abstract

DNA damage activates specific cell signaling cascades for DNA repair, cell cycle arrest, senescence, and/or cell death. Recent studies have demonstrated DNA damage response (DDR) in experimental models of acute kidney injury (AKI). In cisplatin-induced AKI or nephrotoxicity, the DDR pathway of ATR/Chk2/p53 is activated and contributes to renal tubular cell apoptosis. In ischemic AKI, DDR seems more complex and involves at least the ataxia telangiectasia mutated (ATM), a member of the phosphatidylinositol 3-kinase-related kinase (PIKK) family, and p53; however, while ATM may promote DNA repair, p53 may trigger cell death. Targeting DDR for kidney protection in AKI therefore relies on a thorough elucidation of the DDR pathways in various forms of AKI.

Keywords

Acute kidney injury; DNA damage response; cisplatin; renal ischemia/reperfusion

Introduction

DNA, the genetic material within a cell, is constantly challenged by a wide spectrum of genotoxic insults including exogenous and endogenous sources in the process of life (Alexander et al., 2010). Exogenous DNA damage is induced by environmental agents, such

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DISCLOSURES

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as ultraviolet (UV) light and genotoxic chemicals. Endogenous cause of DNA damage, on the other hand, arises from cellular activities such as respiration that releases reactive oxygen species. The main forms of DNA damage include mismatched base pairs, base loss, DNA single-strand breaks (SSBs), and double-strand breaks (DSBs)(Jackson and Bartek, 2009). To safeguard the genome integrity, cells possess an exquisite network called DNA damage response (DDR) to detect DNA lesions, delay cell cycle progression, and promote DNA repair(Ciccia and Elledge, 2010). If this series of events results in a full repair of the DNA lesion, the cell regains the intact genome for living and function; otherwise, unrepaired DNA damage can evoke chronic DDR signaling which leads to cell dysfunction, senescence, or ultimately cell death(Edinger and Thompson, 2004). As such, the sophisticated mechanisms of DNA damage and repair cooperate to determine the fate of affected cells, and defective DDR participates in various human diseases, such as neurodegenerative disorders, immune deficiencies, infertility, cancer, cardiovascular disease, and metabolic syndrome (Alexander et al., 2010; Czarny et al., 2015; Jackson and Bartek, 2009). Emerging evidence has suggested a role of DNA damage and DDR in the pathogenesis of acute kidney injury (AKI). AKI, previously termed acute renal failure, is a clinical syndrome of rapid decline of renal function associated with or caused by injury in kidney tissues. Clinically, the main cause of AKI includes ischemia/reperfusion injury, nephrotoxic damage, and sepsis (Basile et al., 2012; Togel and Westenfelder, 2014; Yang et al., 2016). Using various models of cisplatin-induced nephrotoxic AKI, we and others have delineated a rapid DDR in kidney cells and tissues(Zhu et al., 2015). Moreover, recent studies have begun to unveil DDR and its pathogenic role in renal ischemia/reperfusion injury. This review aims to provide a succinate analysis of these findings to provide the impetus for further elucidation of DDR, the integrated signaling and regulation, and its pathological role in AKI.

DNA damage response

In response to DNA lesions, cells activate an elaborated signaling network, i.e. DDR. In general, DDR can be divided into three major phases that in concert translate the signal of DNA lesions into an integrated cellular response(Jackson and Bartek, 2009) (Figure 1). In the first phase, the “sensors” of DNA lesions detect abnormally structured DNA and initiate the signaling response. The Key DDR sensors known to date in mammalian cells are ATM and ATR (ATM- and Rad-3-related) kinases. Upon activation, these sensor protein kinases phosphorylate the “mediator” proteins that further recruit “transducer” protein kinases, such as checkpoint kinase 1 (Chk1) and checkpoint kinase 2 (Chk2), to amplify the DDR signal. In the final step, the “transducer” kinases phosphorylate their downstream factors called “effectors”, which elicit multiple mechanisms of cell fate determination including DNA repair, cell cycle arrest, and cell death(Marechal and Zou, 2013) (Figure 1).

While sharing some common factors, different types of DNA lesions may activate different DDR. Generally, ATM responds to DNA double-strand breaks (DSB). In the presence of DSB, ATM accumulates to DNA damage site with the help of MRE11/RAD50/NBS1 (MRN) complex via an interaction with the C-terminus of NBS1(Singh et al., 2012). At DNA damage site, ATM rapidly phosphorylates H2AX (a member of H2A histone family) to promote chromatin binding with mediator of damage-checkpoint 1 (MDC1), which can further promote MRN and hence, ATM tethering at DSB. ATM then phosphorylates and

activates the “transducer” Chk2, which, together with ATM, phosphorylates downstream “effectors”, such as p53, resulting in downstream cellular response including DNA repair, cell-cycle arrest, apoptosis, and others(Guevara et al., 2014) (Figure 1). For example, p53 induces p21, an important cyclin-dependent kinase inhibitor, for G1/S phase cell cycle arrest (Megyesi et al., 1998; Zannini et al., 2014) (Figure 1).

On the contrary, ATR often senses single-strand DNA breaks and replication stress due to DNA cross-linking and adduct formation. ATR is recruited to DNA damaged site through ATR-interacting protein (ATRIP). At the damage site, ATR phosphorylates and activates Chk1, which regulates DNA replication in S phase and G2/M transition(Cortez et al., 2001). Specifically, Chk1 phosphorylates and activates cdc25A to regulate CDK1 and CDK2, resulting in G1/S, S, and G2/M phase cell cycle arrest that provides time for DNA repair before replication or mitosis ensues(Pabla et al., 2012) (Figure 1).

Of note, both ATM and ATR may promote DNA repair by enhancing the expression of DNA repair proteins and their accumulation at the DNA lesion site via phosphorylation and associated acetylation, ubiquitination, and/or SUMOylation (Jackson and Bartek, 2009). In addition, emerging evidence suggests that DDR may activate autophagy to protect cells and promote cell survival (Czarny et al., 2015). In this regard, it has been shown that ATM may activate the repressors of mTOR, a major negative regulator of autophagy (Alexander et al., 2010) (Figure 2).

While DDR may activate the above mentioned mechanisms for DNA repair and cell survival, it may also activate the signaling for cell death (Bekker-Jensen and Mailand, 2010). Apoptosis following DNA damage has been well documented, and the underlying mechanisms can be roughly divided into p53-dependent and p53-independent pathways (Figure 2). Upon activation in DDR, p53 may transcriptionally induce the expression of apoptotic genes, such as Bax and PUMA-α, to promote apoptosis. In addition, p53 may directly participate in the activation of the mitochondrial pathway of apoptosis, resulting in cytochrome C release from mitochondria to activate caspases (Roos and Kaina, 2013). A good example of p53-independent pathway of apoptosis in DDR involves c-Abl (Wang, 2000). During mismatch repair, the MMR complex may phosphorylates and activate c-Abl, which can further phosphorylate and activate p73 (a p53 family member) to cause apoptosis (Tsai and Yuan, 2003) (Figure 2). In addition to apoptosis, DNA damage may also induce other forms of cell death, although classical DDR may not be involved. For example, DNA damage induces the activation of poly-(ADP-ribose) polymerase 1 (PARP1), which may trigger necrosis (Shin et al., 2015).

DNA damage response in cisplatin-induced AKI

Cisplatin is one of the most effective chemotherapeutic drugs for the treatment of various types of malignant tumors, such as those of ovary, lung, head, bladder, and many others (Cepeda et al., 2007; Siddik, 2003; Wang and Lippard, 2005). However the usage of cisplatin is limited by its side effects in normal tissues, especially that in kidneys or nephrotoxicity (Arany and Safirstein, 2003; dos Santos et al., 2012; Lebwohl and Canetta, 1998; Miller et al., 2010a; Ozkok and Edelstein, 2014; Pabla and Dong, 2008; Sanchez-

Gonzalez et al., 2011). Cisplatin usually accumulates in renal tubular cells causing the pathologic changes, primarily renal tubular cell injury and death, resulting in AKI(Arany and Safirstein, 2003; Miller et al., 2010b; Oh et al., 2014; Pabla and Dong, 2008). In these cells, cisplatin is converted into a highly reactive molecule following aquation which binds with DNA and form intra-strand and inter-strand cross-linking. The cross-linking unwinds DNA double-helix and interferes with DNA replication and/or transcription, causing replication stress and DNA damage with ensuing DDR and subsequent DNA repair, cell cycle arrest, and cell death(Cepeda et al., 2007; Siddik, 2003; Wang and Lippard, 2005) (Basu and Krishnamurthy, 2010) (Figure 3).

Accumulating evidence indicates that DNA damage and DDR are critical pathogenic mechanisms of AKI induced by cisplatin in kidneys. The initial implication of DDR in cisplatin-AKI was the demonstration of p53 involvement in cisplatin-induced renal tubular cell apoptosis (Cummings and Schnellmann, 2002; Jiang et al., 2004). Interestingly, multiple DDR pathways have now been shown to be altered in cisplatin-induced AKI. During cisplatin treatment of renal tubular cells, there was a rapid activation of ATR, but not ATM or DNA-PK. Notably, suppression of ATR led to the attenuation of p53 activation and apoptosis, supporting a specific role of ATR in cisplatin-induced kidney injury (Pabla et al., 2008). Moreover, this study showed that Chk2, the “transducer” protein kinase downstream of ATR/ATM, was subsequently activated in an ATR-dependent manner to induce p53 activation, which further induces renal cell apoptosis (Pabla et al., 2008). Altogether, these results demonstrate strong evidence that ATR/Chk2/p53 signaling mediates early DNA damage response during cisplatin nephrotoxicity. Intriguingly, ATR activation by cisplatin in renal tubular cells is mainly mediated by mis-match repair proteins, such as MSH2, but not by the classical 9-1-1 protein complex (Pabla et al., 2011b). On the contrary, ATM and associated DDR may play a cytoprotective role in cisplatin nephrotoxicity. In support of this, ATM-deficient cells were shown to be more sensitive to cisplatin-induced apoptosis. In addition, ATM was proteolytically cleaved and inactivated by caspases at the late stage of cisplatin treatment of renal tubular cells, suggesting a mechanism of blocking ATM-mediated cytoprotection for apoptosis (Wang et al., 2006). In a recent study, Kim et al. demonstrated that cisplatin treatment could induce the MRN (Mre11, Rad50, and Nbs1) complex in kidneys, which plays an important role in the process of ATM interaction with DNA lesions (Kim et al., 2015). Thus, in the early phase of cisplatin treatment, ATM may be activated for DNA repair and cell survival, but at the late stage, it is cleaved and inactivated by caspases to facilitate apoptosis. From these studies, however it remains largely unclear whether and how DNA repair is activated and regulated.

In addition to DNA repair, cisplatin may also activate autophagy in the early phase of nephrotoxicity to help cell survival (Figure 3). As a matter of fact, in the first study demonstrating autophagy in cisplatin nephrotoxicity we showed that pifithrin-α, a pharmacological inhibitor of p53, partially suppressed cisplatin-induced autophagy in renal tubular cells (Periyasamy-Thandavan et al., 2008). This and subsequent studies using autophagy-deficient mice further demonstrated a critical role of autophagy in tubular cell survival and kidney protection during cisplatin nephrotoxicity (Jiang et al. 2012; Takahashi et al. 2012). Thus, in cisplatin nephrotoxicity DDR and associated p53 activation may activate both cell death and survival mechanisms (Figure 3). It is generally understood that

the severity of kidney injury or nephrotoxicity determines whether tubular cells die or survive, but it remains elusive how the signaling is tilted from cell survival to cell death as the injury progresses.

Regardless, recent studies have shown that some of pharmacological and genetic approaches that inhibit DDR at various signaling levels have potent therapeutic effects against cisplatin-induced AKI in experimental models(Sahu et al., 2013; Sridevi et al., 2013). For example, in our previous study ATM-deficient cells were prone to developing cisplatin-induced apoptosis, suggesting that functionally ATM cleavage by caspases may diminish the DNA repair or cytoprotective effects of ATM to promote apoptosis (Wang et al., 2006). On the other hand, genetic blockade of ATR /Chk2 signaling ameliorated renal cell injury caused by cisplatin (Pabla et al., 2008). Furthermore, p53 was shown to be a major and critical downstream or effector of DDR during cisplatin-induced AKI(Jiang and Dong, 2008). Comparing with wild-type counterparts, p53 knockout mice showed less apoptosis, lower AKI, and higher survival rate(Wei et al., 2007; Zhang et al., 2014). Thus, in severe cisplatin AKI, DDR is a critical pathogenic mechanism that may be targeted for kidney protection.

DNA damage response in ischemia/reperfusion kidney injury

Renal ischemia/reperfusion (I/R) is a major cause of AKI that is characterized by a rapid decline of renal function and associated with high morbidity, mortality and medical burden (Linkermann et al., 2014; Zuk and Bonventre, 2016). While the pathogenesis of ischemic AKI is multifactorial, recent studies suggest the involvement of DNA damage and DDR.

One DDR activating factor in renal I/R is the reactive oxygen species (ROS). ROS is generated during the reperfusion period of I/R, which induces the formation of 8-oxo-2-deoxyguanosine (8-oxo-dG), a main form of oxidative damage in DNA and apoptosis-associated DNA cleavage (Tsuruya et al., 2003). In the cell, there are two mechanisms to remove 8-oxo-dG, base excision repair (BER) and nucleotide excision repair (NER) (Fu et al. 2012). In BER, 7,8-dihydro-8-oxoguanine DNA glycosylase (OGG1) is the main glycosylase that recognizes and excises 8-oxoG base in nuclear and mitochondrial DNA (mtDNA). Neurons isolated from OGG1-knockout mice were more vulnerable to oxidative insults than wild-type neurons, and compared to wild-type mice, OGG1-knockout mice suffered more severe damage after I/R in brain (Liu et al., 2011), suggesting that OGC1-mediated removal of 8-oxoG is a critical protective mechanism. However, the alkyladenine DNA glycosylase (Aag) mediated base excision may promote, rather than prevent, tissue injury and inflammation during I/R of liver, brain, and kidney (Ebrahimkhani et al., 2014). One possibility is that Aag-mediated base excision may lead to the generation of abasic sites in DNA that induce highly toxic DNA strand breaks followed by PARP1 hyperactivation, cellular bioenergetics failure, and necrosis. For NER, Susa and colleagues reported that Csa −/− and Csb−/− mice with defective NER were less susceptible to renal I/R injury (Susa et al., 2009). To interpret this surprising finding, they suggested that lack of NER may lead to detrimental effects in certain tissues, but it may also elicit adaptive changes in other tissues for them to tolerate pathological insults (Susa et al., 2009).

Our recent work (Ma et al., 2014) examined DDR in renal I/R by analyzing the major components of DDR including ATM, H2AX, Chk2, and p53 during renal I/R using in vivo and vitro models. In this study, DDR was suppressed to different degrees by ATM inhibitor Ku55933, the general caspase inhibitor z-VAD, and the antioxidant N-acetylcysteine, and overexpression of Bcl-2. These observations indicate that multiple mechanisms contribute to the initiation and regulation of DDR during ischemic AKI, including apoptotic DNA fragmentation and oxidative stress. Notably, inhibiting ATM led to an increase in DNA damage shown by H2AX phosphorylation and tubular cell apoptosis, suggesting that ATM may play a cytoprotective role probably by inducing DNA repair(Ma et al., 2014). In line with this inference, ATM deficiency in brain induced significantly higher ROS (Kuang et al., 2012). In addition, p53 as an important effector of DDR apparently plays important roles in ischemic AKI. For example, p53 increased significantly in renal I/R and blockade of p53 ameliorated ischemic AKI (Kelly et al., 2003; Zhang et al., 2014). Together, these studies have implicated DDR in ischemic AKI, although the signaling pathways remain poorly understood. Depending on the severity and stage of AKI, DDR may activate mechanisms for cell survival (DNA repair, cell cycle arrest, and autophagy) and/or cell death (Figure 3)

In addition, DDR may participate in the long-term sequelae of AKI, i.e., renal fibrosis and the progression or transition to chronic kidney disease (CKD). It is known that kidney tissues, especially renal tubules, have an enormous capacity of regeneration or repair (Bonventre and Yang, 2011). As a result, following AKI, if the repair is complete, the kidney may have a full histological and functional recovery. However, frequently the repair is incomplete or maladaptive, resulting in the development of chronic pathologies that are characterized by tubular atrophy, interstitial fibrosis, and inflammation (Venkatachalam et al. 2015). Despite intensive research, the mechanism whereby AKI transits into CKD remains elusive. Nonetheless, there is evidence suggesting the involvement of DDR signaling in post-AKI development of renal fibrosis and AKI-CKD transition (Bonventre, 2014; Guevara et al., 2014). In 2010, Yang and colleagues demonstrated that following AKI, a sub-population of renal tubule cells had G2/M phase cell cycle arrest and, remarkably, these cells were shown to release profibrotic cytokines to induce interstitial fibrosis. Moreover, inhibition of ATM or p53 could reverse the G2/M arrest and suppress profibrotic cytokine production from renal tubular cells, suggesting that DDR may contribute critically to the profibrotic phenotype of renal tubular cells and interstitial fibrogenesis during AKI-CKD transition (Bonventre, 2014; Yang et al., 2010). Collectively, these studies have implicated DNA damage and DDR in ischemic AKI and subsequent renal fibrosis and progression to CKD. However, the current evidence remains sketchy and the pathological role of DDR remains elusive and the regulation largely unknown.

Therapeutic perspectives

With the evidence for the involvement of DNA damage and DDR in AKI, it is logical to consider the therapeutic potential. Obviously, reducing DNA damage would be beneficial. In this regard, it is important to identify the main cause(s) of DNA damage, which may be different according to the causes or types of AKI. For example, cisplatin induces DNA cross-linking and adduct formation followed by replication stress, whereas DNA damage in ischemic AKI may involve ROS, apoptotic injury, and other yet-to-identify factors. In the

case of cisplatin AKI, one effective strategy is to prevent or decrease cisplatin uptake in renal tubular cells by inhibiting relevant transporters, such as organic cation transporters (Oct1, 2) (Ciarimboli et al., 2010) and the copper transporter Ctr1 (Pabla et al., 2009).

In contrast, targeting DDR for therapy is much more complex. The main reason is that DDR may have multiple outcomes, including DNA repair, cell cycle arrest, senescence, and cell death. In injured kidneys, DDR would be beneficial if it stimulates DNA repair; however it would be desirable to suppress DDR if it triggers cell death. Unfortunately, the outcome of DDR in kidneys depends on a variety of factors, such as the severity and types of DNA damage, and cellular context. To complicate matters further, as discussed above several DDR signaling pathways may be activated in the same cells: while one pathway may trigger DNA repair, the other may mainly lead to cell death. Any therapy targeting DDR has to take into account of the delicate balance between these pathways and their associated outcomes. As a result, there may not be a simple or single strategy of targeting DDR for therapeutic purpose in AKI. Because of these considerations, it is very important to elucidate and characterize the DDR signaling network in different types of AKI to provide a guidance for the therapeutic design. Essentially, it is imperative to enhance the DDR pathway of DNA repair and block those that lead to renal cell apoptosis.

As indicated previously (Pabla et al., 2011a; Pabla and Dong, 2008; Pabla and Dong, 2012), targeting DDR in cisplatin AKI for kidney protection has to consider the effect in tumors. It is important to note that overall inhibition of DDR during cisplatin treatment may protect not only kidney cells and tissues but also cancerous cells in tumors and, as a consequence, it may significantly reduce the chemotherapy effect and diminish the whole purpose of cisplatin treatment. In view of this, it is essential to identify the critical differences between the DDR in normal cells and that in malignant cells. For example, p53 is deleted or mutated in over 50% of cancers and the chemotherapy effect of cisplatin in these cancers is therefore independent of p53. In the patients with p53-defective cancers, inhibitors of p53 may protect kidneys without protecting cancer cells or attenuating chemotherapy.

Conclusions

DDR is a biologically significant cellular event that is orchestrated by various signaling cascades leading to DNA repair, cell cycle arrest, senescence, and/or apoptosis. In cisplatin-induced AKI or nephrotoxicity, the DDR pathway consisting of ATR/Chk2/p53 has been delineated and its pathogenic role has been demonstrated. More recent research has begun to unveil DDR in ischemic AKI, which appears to have a more complex signaling network. While targeting DDR holds a promise for kidney protection, it is necessary to test this possibility in various AKI models. Moreover, it is essential to delineate the DDR signaling pathways in a specific AKI model for designing effective strategies of kidney protection.

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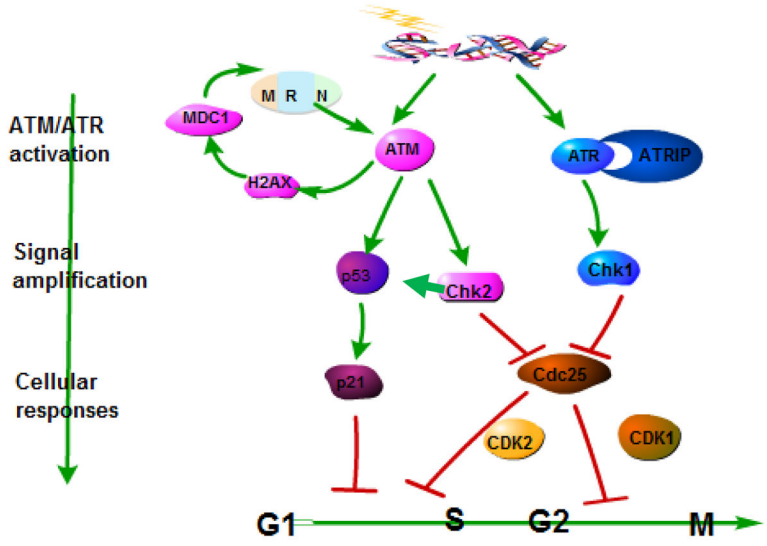

Figure 1. Main signaling pathways of DDR

In response to DNA damage, ATM and ATR kinases are activated via different protein complexes. Then ATM phosphorylates and activates Chk2, which may further induce p53 /p21 for G1/S phase cell cycle arrest. ATR phosphorylates and activates Chk1, which may further induce Cdc25 degradation resulting in the inhibition of CDK1/2 for S phase and G2/M phase cell cycle arrest.

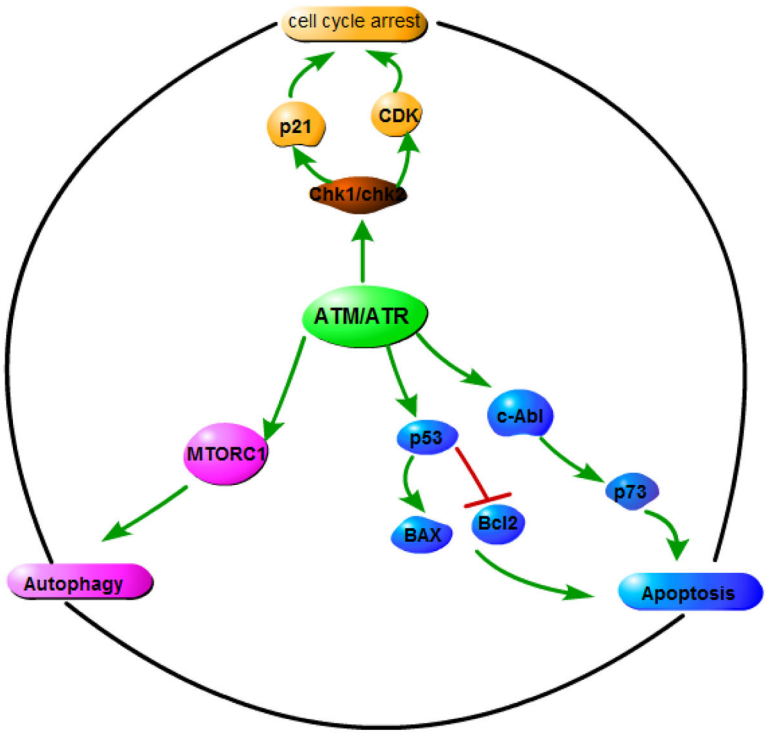

Figure 2. Main pathways leading to autophagy, cell cycle arrest and apoptosis in DDR

In response to DNA damage, ATM and ATR are activated to induce an elaborated signaling network to excute celluar responses such as autophagy, cell cycle arrest, and cell death.

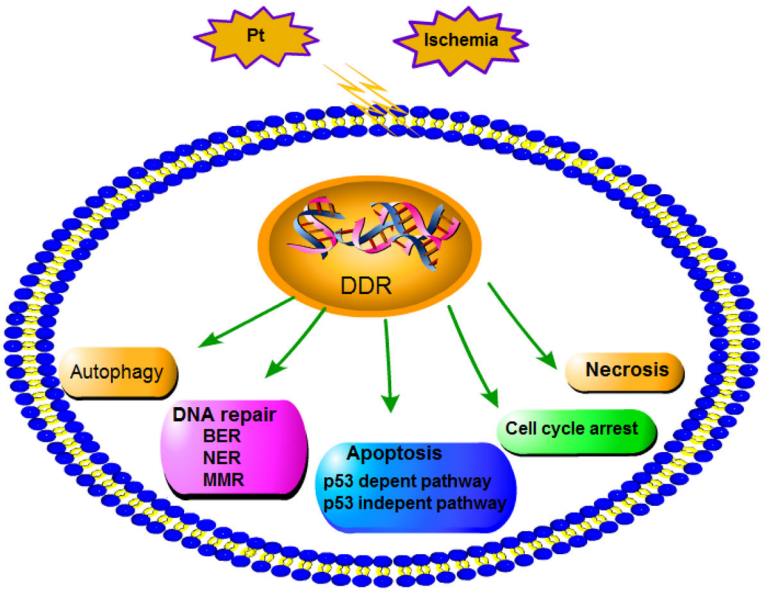

Figure 3. DDR in cell fate determination during cisplatin nephrotoxic and ischemic AKI

Upon activation in AKI, DDR may induce DNA repair, autophagy and cell cycle arrest for cell survival, or it may activate the pathways of cell death including both apoptosis and necrosis.