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Molecular Mechanisms of *H. pylori* Induced DNA Double-Strand Breaks

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ABSTRACT

Infections contribute to carcinogenesis through inflammation-related mechanisms. It is well established that *H. pylori* infection is an etiological factor in gastric carcinogenesis. However, the mechanism through which *H. pylori* infection contributes to the development of gastric cancer has not been fully elucidated. *H. pylori*-associated chronic inflammation is linked to genomic instability via reactive oxygen and nitrogen species (RONS). In this article, we summarize the current knowledge of *H. pylori*-induced double strand breaks (DSBs). Further, we will provide mechanistic insight into how processing of oxidative DNA damage via base excision repair (BER) leads to double strand breaks (DSBs). We review the recent progress how *H. pylori* infection triggers NF-kB /iNOS versus NF-kB/nucleotide excision repair (NER) axis mediated DSBs to drive genomic instability. Taken together, this review discusses current findings related to DSBs and their implications for the mechanisms of DSB repair.

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Introduction

Infection contributes to 20% of cancer worldwide[1]. *H. pylori* infection is one of the most common risk factors for gastric carcinogenesis[2]. More than 50% of the human population is infected with *H. pylori* but few develop gastric cancer[3]. Although some intracellular *H. pylori* has been reported[4,5], this bacterium is generally considered an extracellular pathogen, which has an important role in the pathogenesis of chronic gastritis, peptic ulcers, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[6-8]. Chronic gastritis induced by *H. pylori* represents the first step of a pathological event that can eventually progress to gastric cancer[9,10]. The development of chronic gastritis associated with *H. pylori* infection is a multistage process and is characterized by gastric epithelial cell injury and infiltration inflammatory cells[11]. Numerous virulence factors contribute to host-pathogen interaction that have been described and characterized with an increased risk gastric cancer pathogenesis [6,12]. Those virulence factors enhance the severity of the mucosal inflammatory response, which may largely be responsible for the virulence factor- associated increased risk of gastric cancer[12].

H. pylori, which causes chronic gastritis and contribute to genotoxic activity[13,14]. However, the molecular mechanisms by which *H. pylori* promote genotoxic activity to drive pathogenesis of gastric cancer still need more study. Based on the current knowledge, *H. pylori* infection induces a genotoxic effect via two potential mechanisms. First, *H. pylori* infection enhances infiltration of immune cells including neutrophils and macrophages to produces reactive oxygen species and nitrogen species (RONS)[15]. RONs can cause DNA base damage that leads to single strand

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breaks and enhanced expression of oncogenes [16-18]. Alternatively, RONS activate the oxidant-sensitive transcription factor NF-κB, which induces expression of oncogenes and cell-cycle regulators[19,20]. Activated NF-kB is translocated to the nucleus and forms a protein complex with NER proteins (XPG and XPF) to cleave the promoter regions of the genes and cause DSBs that impact gene expression[21].

H. pylori induces inflammation dependent DNA damage

Chronic inflammation is estimated to contribute to approximately 25% of human cancers[22]. Gastric inflammation in *H. pylori* infection may be induced via two different mechanisms. The first mechanism is initiated via physical contact between the pathogen and the host epithelial cells, either producing direct cell damage or enhancing the ability of epithelial cells to release pro-inflammatory mediators. The second mechanism is likely promoted by *H. pylori* virulence factors (*e.g. CagA, VacA*) that may target potential cell signaling pathways to stimulate immune responses. Interestingly, *H. pylori CagA* positive strain enhances chemokine activation, such as IL-8, a potent neutrophil-activating chemotactic cytokine or chemokine[23,24]. Furthermore, chemokines that are released from infected gastric epithelial cells are able to stimulate neutrophil infiltration and T lymphocytes to enhance RONS mediated gastritis[25,26]. Taken together, *H. pylori* mediated gastric inflammation is associated with humoral and cell-mediated immune cells.

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H. pylori induces BER intermediate dependent DSBs

Chronic inflammatory conditions induce immune and epithelial cells to release RONS, which are capable of causing DNA damage and persistent cellular proliferation[27]. In addition, RONS accumulation may result in proto-oncogene activation, chromosomal aberrations, and DNA mutations[28,29]. However, there is considerable evidence that *H. pylori* itself induces genomic instability and epigenetic alteration in host genome. However, there is little experimental evidence to show the mechanistic insight into how oxidative DNA damage leads to DSBs repair oxidative damaged DNA via BER, which is thought to be the primary repair pathways against oxidative DNA damage[30]. Altogether, the mechanism of *H. pylori*-induced host genomic instability remains poorly understood.

BER is crucial for maintaining genomic stability to prevent carcinogenesis[31-34]. BER is a major DNA repair pathway that removes the majority of oxidative and alkylating DNA damage without affecting the double helix DNA structure[30,35,36]. A tight coordination of the different steps in BER is necessary to avoid genomic instability[37]. BER is initiated by recognition and excision of the damaged base by specific DNA glycosylases. BER is subsequently processed by APE1 and leads to a DNA gaps that are filled by DNA polymerase β (Pol β) and DNA ligase III (LIG3)[38]. Ding et al. have reported live *H. pylori* up-regulated apurinic/apyrimidinic endonuclease1 (APE1) expression in cultured gastric adenocarcinoma cell lines (AGS) and gastric epithelial cells isolated from uninfected human subjects[39]. However, little is known about the role of APE1 expression in *H. pylori*-related gastric diseases. In addition, Taller et al. show that co-culture of *H. pylori* with gastric cancer cell lines induces DSBs

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in a contact-dependent manner[14]. DSBs in those cell lines lead to activation of ATM dependent DNA damage response. *H. pylori*-induced DSBs likely cause chromosomal aberrations, such as deletions, insertions, and translocations, which are a major cause of the loss of heterozygosity.

Oxidative DNA damage levels are increased upon exposure to a variety of environmental factors including *H. pylori* infection [40]. DNA oxidation by RONs can lead to a number of different types of damage, such as 7, 8-hydroxy-2'-deoxyguanosine (8oxodG), abasic sites (AP), and oxidized deoxyribose sugars which in turn lead to SSBs, DSBs[41], and mutation [42,43]. The most common oxidative base modifications resulting from direct attacks by hydroxyl radicals are purine lesions (8oxodG, 8-oxoA) and pyrimidine lesions (thymine glycol and cytosine glycol) are associated with human cancer [44-46]. Oxidized bases, including 8oxodG, are removed predominantly by base excision repair (BER) [47,48]. BER is the major repair pathway of DNA damage induced by RONs and is critical for maintaining genome stability during chronic inflammation that occurs during *H. pylori* infection [49]. BER is initiated by DNA glycosylases that recognize and cleave the damaged bases. Distinct DNA glycosylases recognize specific oxidative lesions and cleave the N-glycosidic bond, releasing the excised DNA damaged base. The resulting abasic site (AP) can then be removed by an apurinic/apyrimidic endonuclease (APE1). The major form of oxidative DNA damage is the formation of 8-oxoG lesions, specifically repaired by the OGG1 DNA glycosylase in mammalian species [48,50]. OGG1 bifunctional DNA glycosylase is the major enzyme that catalyzes the removal of 8oxodG paired with cytosine [51,52]. OGG1 remains bound to its abasic site product and its turnover can be stimulated either by AP

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endonuclease 1 (APE1) or by NEIL1 [53,54], both of which can process the AP site. After AP site processing and end-remodeling, the single-nucleotide gap is filled by Pol β and the nick is sealed by LIG3 to complete repair [55]. Our previously published data show that *H. pylori* infection induces the accumulation of unrepaired BER intermediates that can initiate a cascade of events to generate DSBs [56]. However, *OGG1* deficient mice protect the cells from mutagenic and carcinogenic potential of an accumulation of 8oxoG [57,58]. These mice are viable, do not develop malignancies, and exhibit a spontaneous mutation frequency in liver tissue only two times higher than wild type mice. Furthermore, *OGG1* deficient mice are resistant to *H. pylori* induced inflammation [59]. This low spontaneous mutation rate does not appear consistent with the accumulation of miscoding 8oxoG residues in their genome and suggests the involvement of other DNA repair components [60]. In addition, OGG1 knockout gastric epithelial cells or silencing of an endonuclease functioning as part of the BER machinery, apurinic endonuclease 1 (APE1), failed to affect *H. pylori*-induced DSBs.

DSBs are the principle cytotoxic lesions that can be generated by *H. pylori* infection. They can be caused by accumulation of unrepaired BER intermediates in DNA replication independent manner, and/or they arise when DNA replication forks encounter BER intermediates including DNA single-strand breaks [61,62]. Few studies have shown that accumulation of AP sites in *H. pylori* infected human gastric epithelial cells leads to DSBs [56]. Toller et al. [14] reported that a direct bacterium-host interaction is a prerequisite to DSBs rather than the release of DNA-damaging components. Overall, these results suggest that DSB formation is mediated by BER

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intermediates that are generated from a direct response of the host-bacterium interaction.

NF-kB-iNOS axis dependent DSBs formations

H. pylori infection induces DNA damage on gastric epithelial cells [63].Contact dependent interactions between *H. pylori* bacteria and gastric epithelial cells activate intracellular signaling events that have further downstream effects via activation of the transcription factor NF-κB [64]. In gastrointestinal epithelial cells, NF-κB has a central role in regulating genes that govern the onset of mucosal inflammatory responses following microbial infections [65,66]. NF-κB activation is effected through a series of phosphorylation and transactivation events triggering a downstream signaling pathway that contributes to gastric inflammation in *H. pylori*-infected individuals [67,68]. Activation of NF-κB leads to up-regulation of expression of a variety of inflammatory mediators including IL-8 [69]. This event is essential for the activation of innate and adaptive immune responses against pathogens [65].

NF-κB, which is involved in the regulation of iNOS, has been reported to function as a tumor promoter in inflammation-associated cancer [70,71]. Host response to *H. pylori* infection enhances NF-κB expression in the infiltrating inflammatory cells [72,73], resulting in inducible nitric oxide synthase (iNOS) expression cause 8-nitroguanine and 8-oxodG production in the gastric epithelium [74]. The expression of iNOS mRNA and protein was significantly increased in the epithelial cells of *H. pylori*-positive gastritis patients compared to *H. pylori*-negative patients [74]. The expression of iNOS is responsible for the production of NO that allows inflammatory cells to infiltrate the infected gastric mucosa and submucosa and has been suggested to participate in the

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mutagenic activity associated with the infection [75]. iNOS induces DSBs through NO synthesis [76]. iNOS is an inflammatory mediator that causes the production of NO by macrophages that link chronic inflammation and tumorigenesis [77-79].

Nitric oxide (NO) is often generated in inflammatory conditions due to the induction of NOS in epithelial cells by inflammatory cytokines released from adjacent mononuclear cells [80-82]. iNOS mediated NO enhance inactivation of DNA repair enzymes contribute to genomic instability associated with cancer [78]. NO can directly oxidize DNA, resulting in mutagenic changes [83] and DSBs [76]. Furthermore, NO can nitrosylate thiol and tyrosine residues in susceptible proteins altering their function [84,85]. Although the ability of NO to directly damage DNA has been studied to a limited degree [86], the role of protein nitrosylation in promoting potentially mutagenic changes in DNA has received far less attention. Thus, the effect of iNOS-generated NO on DNA repair proteins is scientifically important to uncover the impact of *H. pylori* triggered iNOS mediated DNA repair defects. Few studies have shown that DNA repair proteins are vulnerable to oxidative damage from NO because of their active sites such as sulphydryl, tyrosine and phenol side chains [87]. DNA repair enzymes such as MGMT, FpyG and PARP with active zinc fingers are potentially inactivated by NO nitrosylation of the thiol moieties of their cysteine-rich residues [88,89]. Taken together, it appears that the integrity of the cell may be challenged during exposure to high concentrations of NO not only by direct oxidative damage to DNA but also by potential NO-mediated disruption of DNA repair enzymes.

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NF-kB-nucleotide excision repair (NER) axis dependent DSBs formation

H. pylori infection increases NF-kB activation to promote inflammatory immune response[90]. Novel mechanisms have recently been described to facilitate transactivation of target genes by introduction of DNA DSBs; one involves the NER endonuclease XPG[91,92], whereas the other requires the activity of topoisomerase 2B (TOP2B)[93]. Endonucleases XPF and XPG are critical components of NER, responsible for excising the damaged DNA strand to remove the DNA lesion. The endonuclease XPG cuts the DNA strand approximately 5-6 nucleotides downstream of 3′ of the DNA damage site. The second incision of this strand, at 20–22 nucleotides upstream of the 5′ of the DNA damage, is performed by the ERCC1-XPF protein complex[94,95]. Although these two endonucleases are recruited and form complexes with NF-kB to make pre-incision complexes, the proper assembly of all the factors seems to be required for dual incision at the promoter region of a given gene. XPF/XPG-mediated DSBs serve to amplify NF-kB target inflammatory gene expression and promote host cell survival[21]. The orchestrated activity of the NF-kB guided XPG and XPF in the formation of the active breaks at the chromatin region of the genome likely promotes a hub that controls gene expression. NER proteins interact with NF-kB and form complex showed a novel mechanism of pathogen-induced transcription-dependent DSB induction and highlights the importance of this mechanism for the amplification of NF-κB target gene transactivation and the survival of *H. pylori*-infected cells. The XPG endonuclease was shown to be recruited to the promoter regions of actively transcribed target genes[92], where it facilitates transcription initiation by

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introducing DSBs and promoting DNA demethylation and gene looping[91]. Silencing of XPG strongly reduced the formation of fragmented DNA upon *H. pylori* infections, suggesting that NER dependent DSBs contribute to genomic instability during infection.

H. pylori impairs DSBs repair

The deleterious effects of DSBs have triggered the evolution of multiple pathways for their repair [96,97]. Homologous recombination (HR) requires sequence homology of extensive DNA regions and repairs of DSBs accurately using information on the undamaged sister chromatid or homologous chromosome. In contrast, non-homologous DNA end-joining (NHEJ), uses no, or extremely limited, sequence homology to rejoin juxtaposed ends in a manner that need not be error free.
If not taken care of properly, they can cause chromosome fragmentation, loss and translocation, possibly resulting in carcinogenesis. *H. pylori* induced DSBs are likely recognized by the MRE11-RAD50-NBS1 (MRN) complex [98,99], which captures the DNA ends, resulting in activation of ataxia telangiectasia mutated kinase (ATM), a member of the phosphatidylinositol 3-kinase-related kinase family [100,101]. Induction of DSBs generates ATM dependent DNA damage response to activate a cascade of effectors to repair the DNA defects. ATM-mediated phosphorylation at serine 139 of the histone H2AX protein (γH2AX) is the critical step to mark the DNA damage sites [102]. ATM is a major molecular sensor of DSBs, directly binds to the damaged DNA and activates DSB repair pathways by phosphorylating target proteins [101,103]. One of the major targets is the MRN complex, which consists of Mre11, Rad50 and NBS1 [104]. This complex has recently been reported to further enhance ATM activation by

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recruiting ATM into the damaged site [105]. Biochemical studies have shown that the Mre11-Rad50-Nbs1 (MRN) complex has nuclease and DNA-unwinding activities as well as DNA-binding and DNA end-bridging properties [106]. After detecting the damage, ATM activates two DSB repair pathways; homologous recombination (HR), and non-homologous end joining (NHEJ). In the NHEJ pathway, DNA-dependent protein kinase (DNA-PK), which consists of DNA-PK catalytic subunit (DNA-PK) and Ku, binds and holds the two ends of the break together. Then ligase IV/XRCC4/XLF carries out the ligation reaction [107] to promote NHEJ. However, *H. pylori*-causes an increase in Ku 70/80 that may indicate NHEJ mediated repair may contribute to genomic instability [108]. Recent evidence has shown that altered DNA-PK and Ku 70/80 are associated with pathological processes in different types of cancer [109]. Moreover, the expression of Ku70 and DNA-PK in *H. pylori*-associated gastritis, intestinal metaplasia and gastric adenoma tissues[110]. Furthermore, Lim et al[111] showed that activated NF-kB-Cox2 axis play a significant role to enhance the expression of KU70/80. In contrast, loss of Ku proteins leads to accumulation of DNA damage that eventually cause cell death in gastric epithelial cells [112].

Our published study shows that DSBs significantly increase in the G1 stage of the cell cycle after *H. pylori* infection [56], suggesting that NHEJ repair may be involved in promotion of error prone repair. When DSBs are generated during S phase at DNA replication forks or after replication in the G2 phase of the cell cycle, HR can contribute to maintain genome integrity. However, activated NFKB/NER during *H. pylori* infection suppress HR proteins and reduce DSBs repair via homologous recombination pathways[21].

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Summary

This review highlights how *H. pylori* associated DNA base damage in infected host cells are likely processed via BER and generate DSBs. *H. pylori* infection contributes to altered BER function and accumulated BER intermediates that can cause DSBs. In additions, this review provides a comprehensive overview how *H. pylori* associated DSBs induced via NF-kB/NER axis and NF-kB/iNOS axis that contributes to influence DNA repair gene expression and enhance genomic instability, and carcinogenesis. During the last few years, remarkable progress has been made in our understanding of the molecular mechanism by which *H. pylori* infection contributes to gastric cancer. However, many questions remain regarding the mechanism of DSBs formation and how those breaks are processed via NHEJ or HR pathways. Does *H. pylori* infection decrease tumor latency for those who are carriers of the genotypes of BER variant? Future studies will likely explore how *H. pylori* manipulate host DNA repair genetics, and how NHEJ processes the DSBs.

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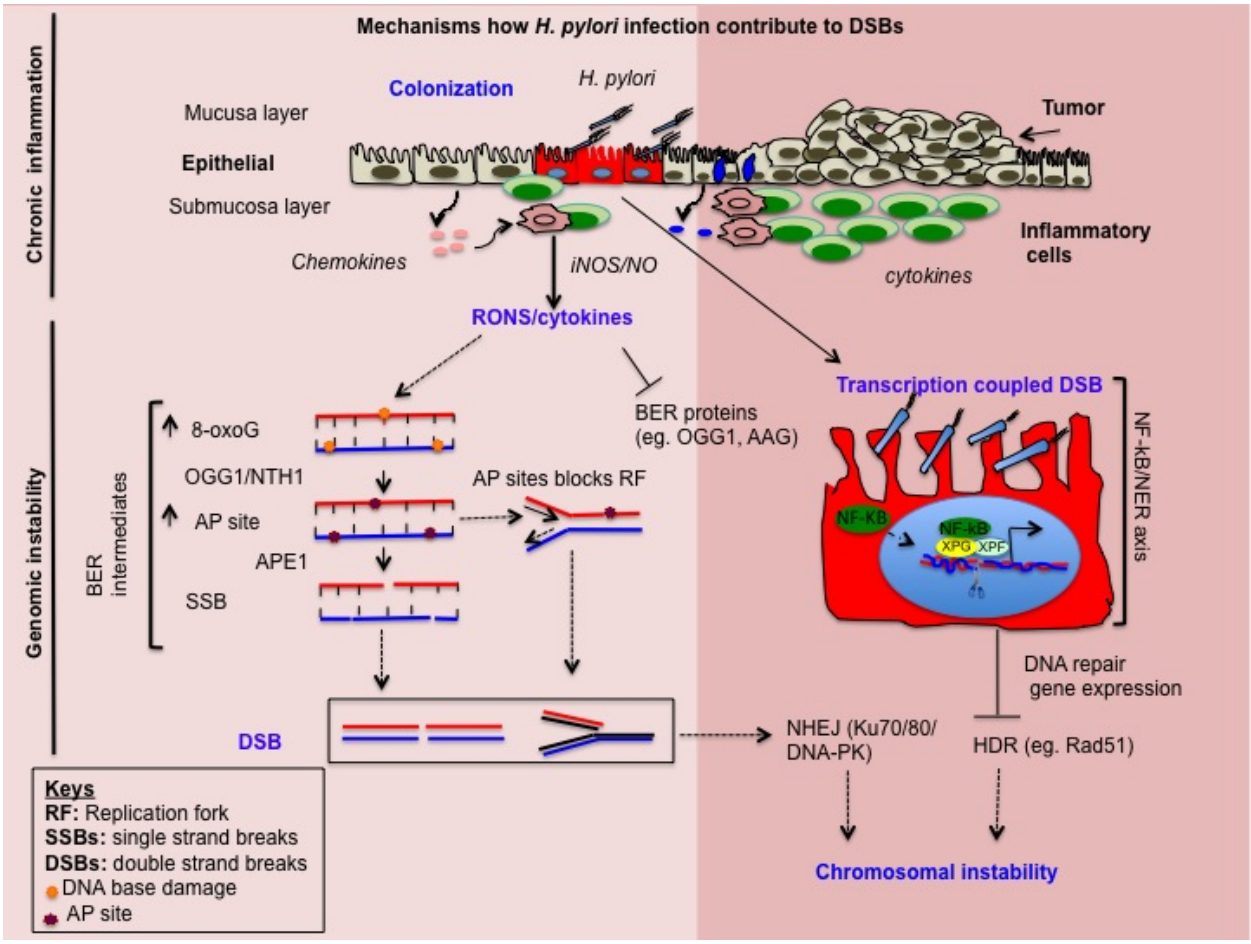

Figure 1. Molecular mechanisms of *H. pylori* induced DSBs. Schematic representation of how *H. pylori* induces DSBs. *H. pylori* infection causes DNA damage in gastric epithelial cells[63]. *H. pylori*-host cell interaction is a prerequisite for DSBs[113] (top panel). Persistence of interaction host-bacterium leads to chronic inflammation and release of inflammatory cytokines and chemokines that contribute to oxidative DNA damage that is processed via BER pathways (bottom panel). Processing oxidative DNA damage by DNA glycosylase (eg. OGG1, NTH1, NEIL1 *etc*) contributes to accumulation of apurinic/apyrimidinic (AP) sites that are eventually converted to DSBs[56]. In addition, some of the cytokines (eg. TNF-α) inhibit the BER proteins to exacerbate genomic instability. The second pathways associated with *H. pylori*

mediated NF-kB activation leads to formation of a protein complex with nucleotide excision repair proteins (XPF and XPG), cleaves the promoter regions, and alters gene expression[13] including HR DNA repair proteins (Rad51). Alternatively, NF-kB/ iNOS/mediated NO production leads to DNA damage and /or inhibit DNA repair proteins (AAG) that is likely impact BER and causes DSBs.

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References

1. Kuper, H.; Adami, H.O.; Trichopoulos, D. Infections as a major preventable cause of human cancer. *J Intern Med* **2000**, *248*, 171-183.
2. de Martel, C.; Forman, D.; Plummer, M. Gastric cancer: Epidemiology and risk factors. *Gastroenterol Clin North Am* **2013**, *42*, 219-240.
3. Peek, R.M., Jr.; Blaser, M.J. Helicobacter pylori and gastrointestinal tract adenocarcinomas. *Nat Rev Cancer* **2002**, *2*, 28-37.
4. Amieva, M.R.; Salama, N.R.; Tompkins, L.S.; Falkow, S. Helicobacter pylori enter and survive within multivesicular vacuoles of epithelial cells. *Cell Microbiol* **2002**, *4*, 677-690.

5. Kwok, T.; Backert, S.; Schwarz, H.; Berger, J.; Meyer, T.F. Specific entry of helicobacter pylori into cultured gastric epithelial cells via a zipper-like mechanism. *Infect Immun* **2002**, *70*, 2108-2120.

6. Covacci, A.; Telford, J.L.; Del Giudice, G.; Parsonnet, J.; Rappuoli, R. Helicobacter pylori virulence and genetic geography. *Science* **1999**, *284*, 1328-1333.

7. Montecucco, C.; Rappuoli, R. Living dangerously: How helicobacter pylori survives in the human stomach. *Nature reviews. Molecular cell biology* **2001**, *2*, 457-466.

8. Monack, D.M.; Mueller, A.; Falkow, S. Persistent bacterial infections: The interface of the pathogen and the host immune system. *Nat Rev Microbiol* **2004**, *2*, 747-765.

9. Correa, P. Human gastric carcinogenesis: A multistep and multifactorial process--first american cancer society award lecture on cancer epidemiology and prevention. *Cancer Res* **1992**, *52*, 6735-6740.

10. Ohnishi, N.; Yuasa, H.; Tanaka, S.; Sawa, H.; Miura, M.; Matsui, A.; Higashi, H.; Musashi, M.; Iwabuchi, K.; Suzuki, M., *et al.* Transgenic expression of helicobacter pylori caga induces gastrointestinal and hematopoietic neoplasms in mouse. *Proc Natl Acad Sci U S A* **2008**, *105*, 1003-1008.

11. Smoot, D.T.; Wynn, Z.; Elliott, T.B.; Allen, C.R.; Mekasha, G.; Naab, T.; Ashktorab, H. Effects of helicobacter pylori on proliferation of gastric epithelial cells in vitro. *Am J Gastroenterol* **1999**, *94*, 1508-1511.

12. Dubreuil, J.D.; Giudice, G.D.; Rappuoli, R. Helicobacter pylori interactions with host serum and extracellular matrix proteins: Potential role in the infectious process. *Microbiol Mol Biol Rev* **2002**, *66*, 617-629, table of contents.

13. Hartung, M.L.; Gruber, D.C.; Koch, K.N.; Gruter, L.; Rehrauer, H.; Tegtmeyer, N.; Backert, S.; Muller, A. H. Pylori-induced DNA strand breaks are introduced by nucleotide excision repair endonucleases and promote nf-kappab target gene expression. *Cell Rep* **2015**, *13*, 70-79.

14. Toller, I.M.; Neelsen, K.J.; Steger, M.; Hartung, M.L.; Hottiger, M.O.; Stucki, M.; Kalali, B.; Gerhard, M.; Sartori, A.A.; Lopes, M.*, et al.* Carcinogenic bacterial pathogen helicobacter pylori triggers DNA double-strand breaks and a DNA damage response in its host cells. *Proc Natl Acad Sci U S A* **2011**, *108*, 14944-14949.

15. Suzuki, M.; Miura, S.; Mori, M.; Kai, A.; Suzuki, H.; Fukumura, D.; Suematsu, M.; Tsuchiya, M. Rebamipide, a novel antiulcer agent, attenuates helicobacter pylori induced gastric mucosal cell injury associated with neutrophil derived oxidants. *Gut* **1994**, *35*, 1375-1378.

16. Cerutti, P.A. Oxy-radicals and cancer. *Lancet* **1994**, *344*, 862-863.

17. Feig, D.I.; Reid, T.M.; Loeb, L.A. Reactive oxygen species in tumorigenesis. *Cancer Res* **1994**, *54*, 1890s-1894s.

18. Schreck, R.R. Tumor suppressor gene (rb and p53) mutations in osteosarcoma. *Pediatric hematology and oncology* **1992**, *9*, ix-x.

19. D'Angio, C.T.; Finkelstein, J.N. Oxygen regulation of gene expression: A study in opposites. *Mol Genet Metab* **2000**, *71*, 371-380.

20. Adler, V.; Yin, Z.; Tew, K.D.; Ronai, Z. Role of redox potential and reactive oxygen species in stress signaling. *Oncogene* **1999**, *18*, 6104-6111.

21. Hartung, M.L.; Gruber, D.C.; Koch, K.N.; Gruter, L.; Rehrauer, H.; Tegtmeyer, N.; Backert, S.; Muller, A. H. Pylori-induced DNA strand breaks are introduced by nucleotide excision repair endonucleases and promote nf-kappab target gene expression. *Cell Rep* **2015**, *13*, 70-79.

22. Kawanishi, S.; Ohnishi, S.; Ma, N.; Hiraku, Y.; Murata, M. Crosstalk between DNA damage and inflammation in the multiple steps of carcinogenesis. *Int J Mol Sci* **2017**, *18*.

23. Eck, M.; Schmausser, B.; Scheller, K.; Toksoy, A.; Kraus, M.; Menzel, T.; Muller-Hermelink, H.K.; Gillitzer, R. Cxc chemokines gro(alpha)/il-8 and ip-10/mig in helicobacter pylori gastritis. *Clin Exp Immunol* **2000**, *122*, 192-199.

24. Watanabe, N.; Shimada, T.; Ohtsuka, Y.; Hiraishi, H.; Terano, A. Proinflammatory cytokines and helicobacter pylori stimulate cc-chemokine expression in gastric epithelial cells. *J Physiol Pharmacol* **1997**, *48*, 405-413.

25. Nozawa, Y.; Nishihara, K.; Peek, R.M.; Nakano, M.; Uji, T.; Ajioka, H.; Matsuura, N.; Miyake, H. Identification of a signaling cascade for interleukin-8 production by helicobacter pylori in human gastric epithelial cells. *Biochem Pharmacol* **2002**, *64*, 21-30.

26. Naito, Y.; Yoshikawa, T. Molecular and cellular mechanisms involved in helicobacter pylori-induced inflammation and oxidative stress. *Free Radic Biol Med* **2002**, *33*, 323-336.

27. Perryman, S.V.; Sylvester, K.G. Repair and regeneration: Opportunities for carcinogenesis from tissue stem cells. *J Cell Mol Med* **2006**, *10*, 292-308.

28. Floyd, R.A. Role of oxygen free radicals in carcinogenesis and brain ischemia. *FASEB J* **1990**, *4*, 2587-2597.

29. Du, M.Q.; Carmichael, P.L.; Phillips, D.H. Induction of activating mutations in the human c-ha-ras-1 proto-oncogene by oxygen free radicals. *Mol Carcinog* **1994**, *11*, 170-175.

30. Dianov, G.L.; Hubscher, U. Mammalian base excision repair: The forgotten archangel. *Nucleic Acids Res* **2013**, *41*, 3483-3490.

31. Al-Tassan, N.; Chmiel, N.H.; Maynard, J.; Fleming, N.; Livingston, A.L.; Williams, G.T.; Hodges, A.K.; Davies, D.R.; David, S.S.; Sampson, J.R., *et al.* Inherited variants of myh associated with somatic g:C-->t:A mutations in colorectal tumors. *Nat Genet* **2002**, *30*, 227-232.

32. Farrington, S.M.; Tenesa, A.; Barnetson, R.; Wiltshire, A.; Prendergast, J.; Porteous, M.; Campbell, H.; Dunlop, M.G. Germline susceptibility to colorectal cancer due to base-excision repair gene defects. *Am J Hum Genet* **2005**, *77*, 112-119.

33. Mahjabeen, I.; Masood, N.; Baig, R.M.; Sabir, M.; Inayat, U.; Malik, F.A.; Kayani, M.A. Novel mutations of ogg1 base excision repair pathway gene in laryngeal cancer patients. *Fam Cancer* **2012**, *11*, 587-593.

34. Shinmura, K.; Tao, H.; Goto, M.; Igarashi, H.; Taniguchi, T.; Maekawa, M.; Takezaki, T.; Sugimura, H. Inactivating mutations of the human base excision repair gene neil1 in gastric cancer. *Carcinogenesis* **2004**, *25*, 2311-2317.

35. Kim, Y.J.; Wilson, D.M., 3rd. Overview of base excision repair biochemistry. *Curr Mol Pharmacol* **2012**, *5*, 3-13.

36. Wallace, S.S.; Murphy, D.L.; Sweasy, J.B. Base excision repair and cancer. *Cancer Lett* **2012**, *327*, 73-89.

37. Allinson, S.L.; Sleeth, K.M.; Matthewman, G.E.; Dianov, G.L. Orchestration of base excision repair by controlling the rates of enzymatic activities. *DNA repair* **2004**, *3*, 23-31.

38. Robertson, A.B.; Klungland, A.; Rognes, T.; Leiros, I. DNA repair in mammalian cells: Base excision repair: The long and short of it. *Cellular and molecular life sciences : CMLS* **2009**, *66*, 981-993.

39. Ding, S.Z.; O'Hara, A.M.; Denning, T.L.; Dirden-Kramer, B.; Mifflin, R.C.; Reyes, V.E.; Ryan, K.A.; Elliott, S.N.; Izumi, T.; Boldogh, I.*, et al.* Helicobacter pylori and h2o2 increase ap endonuclease-1/redox factor-1 expression in human gastric epithelial cells. *Gastroenterology* **2004**, *127*, 845-858.

40. Lindahl, T. Instability and decay of the primary structure of DNA. *Nature* **1993**, *362*, 709-715.

41. Cooke, M.S.; Evans, M.D.; Dizdaroglu, M.; Lunec, J. Oxidative DNA damage: Mechanisms, mutation, and disease. *FASEB J* **2003**, *17*, 1195-1214.

42. Kim, J.J.; Tao, H.; Carloni, E.; Leung, W.K.; Graham, D.Y.; Sepulveda, A.R. Helicobacter pylori impairs DNA mismatch repair in gastric epithelial cells. *Gastroenterology* **2002**, *123*, 542-553.

 doi:10.20944/preprints201808.0291.v1

43. Park, D.I.; Park, S.H.; Kim, S.H.; Kim, J.W.; Cho, Y.K.; Kim, H.J.; Sohn, C.I.; Jeon, W.K.; Kim, B.I.; Cho, E.Y., *et al.* Effect of helicobacter pylori infection on the expression of DNA mismatch repair protein. *Helicobacter* **2005**, *10*, 179-184.

44. Teoule, R.; Bert, C.; Bonicel, A. Thymine fragment damage retained in the DNA polynucleotide chain after gamma irradiation in aerated solutions. Ii. *Radiation research* **1977**, *72*, 190-200.

45. Altieri, F.; Grillo, C.; Maceroni, M.; Chichiarelli, S. DNA damage and repair: From molecular mechanisms to health implications. *Antioxidants & redox signaling* **2008**, *10*, 891-937.

46. Grollman, A.P.; Moriya, M. Mutagenesis by 8-oxoguanine: An enemy within. *Trends in genetics : TIG* **1993**, *9*, 246-249.

47. Demple, B.; Harrison, L. Repair of oxidative damage to DNA: Enzymology and biology. *Annu Rev Biochem* **1994**, *63*, 915-948.

48. Aburatani, H.; Hippo, Y.; Ishida, T.; Takashima, R.; Matsuba, C.; Kodama, T.; Takao, M.; Yasui, A.; Yamamoto, K.; Asano, M. Cloning and characterization of mammalian 8-hydroxyguanine-specific DNA glycosylase/apurinic, apyrimidinic lyase, a functional mutm homologue. *Cancer Res* **1997**, *57*, 2151-2156.

49. Meira, L.B.; Bugni, J.M.; Green, S.L.; Lee, C.W.; Pang, B.; Borenshtein, D.; Rickman, B.H.; Rogers, A.B.; Moroski-Erkul, C.A.; McFaline, J.L., *et al.* DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. *J Clin Invest* **2008**, *118*, 2516-2525.

50. Radicella, J.P.; Dherin, C.; Desmaze, C.; Fox, M.S.; Boiteux, S. Cloning and characterization of hogg1, a human homolog of the ogg1 gene of saccharomyces cerevisiae. *Proc Natl Acad Sci U S A* **1997**, *94*, 8010-8015.

51. Fortini, P.; Parlanti, E.; Sidorkina, O.M.; Laval, J.; Dogliotti, E. The type of DNA glycosylase determines the base excision repair pathway in mammalian cells. *J Biol Chem* **1999**, *274*, 15230-15236.

52. Nishimura, S. Involvement of mammalian ogg1(mmh) in excision of the 8-hydroxyguanine residue in DNA. *Free Radic Biol Med* **2002**, *32*, 813-821.

53. Mokkapati, S.K.; Wiederhold, L.; Hazra, T.K.; Mitra, S. Stimulation of DNA glycosylase activity of ogg1 by neil1: Functional collaboration between two human DNA glycosylases. *Biochemistry* **2004**, *43*, 11596-11604.

54. Sidorenko, V.S.; Nevinsky, G.A.; Zharkov, D.O. Mechanism of interaction between human 8-oxoguanine-DNA glycosylase and ap endonuclease. *DNA repair* **2007**, *6*, 317-328.

55. Fortini, P.; Pascucci, B.; Parlanti, E.; D'Errico, M.; Simonelli, V.; Dogliotti, E. The base excision repair: Mechanisms and its relevance for cancer susceptibility. *Biochimie* **2003**, *85*, 1053-1071.

56. Kidane, D.; Murphy, D.L.; Sweasy, J.B. Accumulation of abasic sites induces genomic instability in normal human gastric epithelial cells during helicobacter pylori infection. *Oncogenesis* **2014**, *3*, e128.

57. Klungland, A.; Rosewell, I.; Hollenbach, S.; Larsen, E.; Daly, G.; Epe, B.; Seeberg, E.; Lindahl, T.; Barnes, D.E. Accumulation of premutagenic DNA

lesions in mice defective in removal of oxidative base damage. *Proc Natl Acad Sci U S A* **1999**, *96*, 13300-13305.

58. Minowa, O.; Arai, T.; Hirano, M.; Monden, Y.; Nakai, S.; Fukuda, M.; Itoh, M.; Takano, H.; Hippou, Y.; Aburatani, H.*, et al.* Mmh/ogg1 gene inactivation results in accumulation of 8-hydroxyguanine in mice. *Proc Natl Acad Sci U S A* **2000**, *97*, 4156-4161.

59. Touati, E.; Michel, V.; Thiberge, J.M.; Ave, P.; Huerre, M.; Bourgade, F.; Klungland, A.; Labigne, A. Deficiency in ogg1 protects against inflammation and mutagenic effects associated with h. Pylori infection in mouse. *Helicobacter* **2006**, *11*, 494-505.

60. Arai, T.; Kelly, V.P.; Minowa, O.; Noda, T.; Nishimura, S. High accumulation of oxidative DNA damage, 8-hydroxyguanine, in mmh/ogg1 deficient mice by chronic oxidative stress. *Carcinogenesis* **2002**, *23*, 2005-2010.

61. Khanna, K.K.; Jackson, S.P. DNA double-strand breaks: Signaling, repair and the cancer connection. *Nat Genet* **2001**, *27*, 247-254.

62. Mills, K.D.; Ferguson, D.O.; Alt, F.W. The role of DNA breaks in genomic instability and tumorigenesis. *Immunol Rev* **2003**, *194*, 77-95.

63. Obst, B.; Wagner, S.; Sewing, K.F.; Beil, W. Helicobacter pylori causes DNA damage in gastric epithelial cells. *Carcinogenesis* **2000**, *21*, 1111-1115.

64. Maeda, S.; Yoshida, H.; Ogura, K.; Mitsuno, Y.; Hirata, Y.; Yamaji, Y.; Akanuma, M.; Shiratori, Y.; Omata, M. H. Pylori activates nf-kappab through a signaling pathway involving ikappab kinases, nf-kappab-inducing kinase, traf2, and traf6 in gastric cancer cells. *Gastroenterology* **2000**, *119*, 97-108.

65. Lamb, A.; Chen, L.F. The many roads traveled by helicobacter pylori to nfkappab activation. *Gut Microbes* **2010**, *1*, 109-113.

66. Orlowski, R.Z.; Baldwin, A.S., Jr. Nf-kappab as a therapeutic target in cancer. *Trends Mol Med* **2002**, *8*, 385-389.

67. Bhattacharyya, A.; Pathak, S.; Kundu, M.; Basu, J. Mitogen-activated protein kinases regulate mycobacterium avium-induced tumor necrosis factor-alpha release from macrophages. *FEMS Immunol Med Microbiol* **2002**, *34*, 73-80.

68. Hayden, M.S.; Ghosh, S. Shared principles in nf-kappab signaling. *Cell* **2008**, *132*, 344-362.

69. De Luca, A.; Iaquinto, G. Helicobacter pylori and gastric diseases: A dangerous association. *Cancer Lett* **2004**, *213*, 1-10.

70. Pikarsky, E.; Porat, R.M.; Stein, I.; Abramovitch, R.; Amit, S.; Kasem, S.; Gutkovich-Pyest, E.; Urieli-Shoval, S.; Galun, E.; Ben-Neriah, Y. Nf-kappab functions as a tumour promoter in inflammation-associated cancer. *Nature* **2004**, *431*, 461-466.

71. Oussaief, L.; Ramirez, V.; Hippocrate, A.; Arbach, H.; Cochet, C.; Proust, A.; Raphael, M.; Khelifa, R.; Joab, I. Nf-kappab-mediated modulation of inducible nitric oxide synthase activity controls induction of the epstein-barr virus productive cycle by transforming growth factor beta 1. *J Virol* **2011**, *85*, 6502-6512.

72. Viala, J.; Chaput, C.; Boneca, I.G.; Cardona, A.; Girardin, S.E.; Moran, A.P.; Athman, R.; Memet, S.; Huerre, M.R.; Coyle, A.J.*, et al.* Nod1 responds to

peptidoglycan delivered by the helicobacter pylori cag pathogenicity island. *Nat Immunol* **2004**, *5*, 1166-1174.

73. Brandt, S.; Kwok, T.; Hartig, R.; Konig, W.; Backert, S. Nf-kappab activation and potentiation of proinflammatory responses by the helicobacter pylori caga protein. *Proc Natl Acad Sci U S A* **2005**, *102*, 9300-9305.
74. Rieder, G.; Hofmann, J.A.; Hatz, R.A.; Stolte, M.; Enders, G.A. Up-regulation of inducible nitric oxide synthase in helicobacter pylori-associated gastritis may represent an increased risk factor to develop gastric carcinoma of the intestinal type. *Int J Med Microbiol* **2003**, *293*, 403-412.
75. Touati, E.; Michel, V.; Thiberge, J.M.; Wuscher, N.; Huerre, M.; Labigne, A. Chronic helicobacter pylori infections induce gastric mutations in mice. *Gastroenterology* **2003**, *124*, 1408-1419.
76. Baydoun, H.H.; Cherian, M.A.; Green, P.; Ratner, L. Inducible nitric oxide synthase mediates DNA double strand breaks in human t-cell leukemia virus type 1-induced leukemia/lymphoma. *Retrovirology* **2015**, *12*, 71.
77. Lowenstein, C.J.; Padalko, E. Inos (nos2) at a glance. *J Cell Sci* **2004**, *117*, 2865-2867.
78. Choudhari, S.K.; Chaudhary, M.; Bagde, S.; Gadbail, A.R.; Joshi, V. Nitric oxide and cancer: A review. *World J Surg Oncol* **2013**, *11*, 118.
79. Thomsen, L.L.; Lawton, F.G.; Knowles, R.G.; Beesley, J.E.; Riveros-Moreno, V.; Moncada, S. Nitric oxide synthase activity in human gynecological cancer. *Cancer Res* **1994**, *54*, 1352-1354.

80. Geem, D.; Medina-Contreras, O.; Kim, W.; Huang, C.S.; Denning, T.L. Isolation and characterization of dendritic cells and macrophages from the mouse intestine. *J Vis Exp* **2012**, e4040.

81. Geller, D.A.; Di Silvio, M.; Nussler, A.K.; Wang, S.C.; Shapiro, R.A.; Simmons, R.L.; Billiar, T.R. Nitric oxide synthase expression is induced in hepatocytes in vivo during hepatic inflammation. *J Surg Res* **1993**, *55*, 427-432.

82. Nussler, A.K.; Geller, D.A.; Sweetland, M.A.; Di Silvio, M.; Billiar, T.R.; Madariaga, J.B.; Simmons, R.L.; Lancaster, J.R., Jr. Induction of nitric oxide synthesis and its reactions in cultured human and rat hepatocytes stimulated with cytokines plus lps. *Biochem Biophys Res Commun* **1993**, *194*, 826-835.

83. Wink, D.A.; Kasprzak, K.S.; Maragos, C.M.; Elespuru, R.K.; Misra, M.; Dunams, T.M.; Cebula, T.A.; Koch, W.H.; Andrews, A.W.; Allen, J.S., *et al.* DNA deaminating ability and genotoxicity of nitric oxide and its progenitors. *Science* **1991**, *254*, 1001-1003.

84. Ischiropoulos, H.; Zhu, L.; Beckman, J.S. Peroxynitrite formation from macrophage-derived nitric oxide. *Arch Biochem Biophys* **1992**, *298*, 446-451.

85. Kong, S.K.; Yim, M.B.; Stadtman, E.R.; Chock, P.B. Peroxynitrite disables the tyrosine phosphorylation regulatory mechanism: Lymphocyte-specific tyrosine kinase fails to phosphorylate nitrated cdc2(6-20)nh2 peptide. *Proc Natl Acad Sci U S A* **1996**, *93*, 3377-3382.

86. Nguyen, T.; Brunson, D.; Crespi, C.L.; Penman, B.W.; Wishnok, J.S.; Tannenbaum, S.R. DNA damage and mutation in human cells exposed to nitric oxide in vitro. *Proc Natl Acad Sci U S A* **1992**, *89*, 3030-3034.

 doi:10.20944/preprints201808.0291.v1

87. Starke, D.W.; Chen, Y.; Bapna, C.P.; Lesnefsky, E.J.; Mieyal, J.J. Sensitivity of protein sulfhydryl repair enzymes to oxidative stress. *Free Radic Biol Med* **1997**, *23*, 373-384.

88. Wink, D.A.; Laval, J. The fpg protein, a DNA repair enzyme, is inhibited by the biomediator nitric oxide in vitro and in vivo. *Carcinogenesis* **1994**, *15*, 2125-2129.

89. O'Connor, T.R.; Graves, R.J.; de Murcia, G.; Castaing, B.; Laval, J. Fpg protein of escherichia coli is a zinc finger protein whose cysteine residues have a structural and/or functional role. *J Biol Chem* **1993**, *268*, 9063-9070.

90. Telford, J.L.; Covacci, A.; Rappuoli, R.; Chiara, P. Immunobiology of helicobacter pylori infection. *Curr Opin Immunol* **1997**, *9*, 498-503.

91. Le May, N.; Fradin, D.; Iltis, I.; Bougneres, P.; Egly, J.M. Xpg and xpf endonucleases trigger chromatin looping and DNA demethylation for accurate expression of activated genes. *Mol Cell* **2012**, *47*, 622-632.

92. Le May, N.; Mota-Fernandes, D.; Velez-Cruz, R.; Iltis, I.; Biard, D.; Egly, J.M. Ner factors are recruited to active promoters and facilitate chromatin modification for transcription in the absence of exogenous genotoxic attack. *Mol Cell* **2010**, *38*, 54-66.

93. Haffner, M.C.; Aryee, M.J.; Toubaji, A.; Esopi, D.M.; Albadine, R.; Gurel, B.; Isaacs, W.B.; Bova, G.S.; Liu, W.; Xu, J.*, et al.* Androgen-induced top2b-mediated double-strand breaks and prostate cancer gene rearrangements. *Nat Genet* **2010**, *42*, 668-675.

94. Leibeling, D.; Laspe, P.; Emmert, S. Nucleotide excision repair and cancer. *J Mol Histol* **2006**, *37*, 225-238.

95. Friedberg, E.C. How nucleotide excision repair protects against cancer. *Nat Rev Cancer* **2001**, *1*, 22-33.

96. Ivanov, E.L.; Haber, J.E. DNA repair: Rad alert. *Curr Biol* **1997**, *7*, R492-495.

97. Kanaar, R.; Hoeijmakers, J.H. Recombination and joining: Different means to the same ends. *Genes Funct* **1997**, *1*, 165-174.

98. Matsuura, S.; Tauchi, H.; Nakamura, A.; Kondo, N.; Sakamoto, S.; Endo, S.; Smeets, D.; Solder, B.; Belohradsky, B.H.; Der Kaloustian, V.M.*, et al.* Positional cloning of the gene for nijmegen breakage syndrome. *Nat Genet* **1998**, *19*, 179-181.

99. Carney, J.P.; Maser, R.S.; Olivares, H.; Davis, E.M.; Le Beau, M.; Yates, J.R., 3rd; Hays, L.; Morgan, W.F.; Petrini, J.H. The hmre11/hrad50 protein complex and nijmegen breakage syndrome: Linkage of double-strand break repair to the cellular DNA damage response. *Cell* **1998**, *93*, 477-486.

100. Stracker, T.H.; Petrini, J.H. The mre11 complex: Starting from the ends. *Nature reviews. Molecular cell biology* **2011**, *12*, 90-103.

101. Shiloh, Y.; Lehmann, A.R. Maintaining integrity. *Nat Cell Biol* **2004**, *6*, 923-928.

102. Burma, S.; Chen, B.P.; Murphy, M.; Kurimasa, A.; Chen, D.J. Atm phosphorylates histone h2ax in response to DNA double-strand breaks. *J Biol Chem* **2001**, *276*, 42462-42467.

103. Bakkenist, C.J.; Kastan, M.B. Phosphatases join kinases in DNA-damage response pathways. *Trends Cell Biol* **2004**, *14*, 339-341.

104. Williams, R.S.; Williams, J.S.; Tainer, J.A. Mre11-rad50-nbs1 is a keystone complex connecting DNA repair machinery, double-strand break signaling, and the chromatin template. *Biochem Cell Biol* **2007**, *85*, 509-520.

105. Dupre, A.; Boyer-Chatenet, L.; Gautier, J. Two-step activation of atm by DNA and the mre11-rad50-nbs1 complex. *Nat Struct Mol Biol* **2006**, *13*, 451-457.

106. D'Amours, D.; Jackson, S.P. The mre11 complex: At the crossroads of dna repair and checkpoint signalling. *Nature reviews. Molecular cell biology* **2002**, *3*, 317-327.

107. Ahnesorg, P.; Smith, P.; Jackson, S.P. Xlf interacts with the xrcc4-DNA ligase iv complex to promote DNA nonhomologous end-joining. *Cell* **2006**, *124*, 301-313.

108. Bae, M.; Lim, J.W.; Kim, H. Oxidative DNA damage response in helicobacter pylori-infected mongolian gerbils. *J Cancer Prev* **2013**, *18*, 271-275.

109. Abe, T.; Ishiai, M.; Hosono, Y.; Yoshimura, A.; Tada, S.; Adachi, N.; Koyama, H.; Takata, M.; Takeda, S.; Enomoto, T.*, et al.* Ku70/80, DNA-pkcs, and artemis are essential for the rapid induction of apoptosis after massive dsb formation. *Cellular signalling* **2008**, *20*, 1978-1985.

110. Lee, H.S.; Choe, G.; Park, K.U.; Park, D.J.; Yang, H.K.; Lee, B.L.; Kim, W.H. Altered expression of DNA-dependent protein kinase catalytic subunit (DNA-pkcs) during gastric carcinogenesis and its clinical implications on gastric cancer. *Int J Oncol* **2007**, *31*, 859-866.

111. Lim, J.W.; Kim, H.; Kim, K.H. Expression of ku70 and ku80 mediated by nf-kappa b and cyclooxygenase-2 is related to proliferation of human gastric cancer cells. *J Biol Chem* **2002**, *277*, 46093-46100.

 doi:10.20944/preprints201808.0291.v1

112. Song, J.Y.; Lim, J.W.; Kim, H.; Morio, T.; Kim, K.H. Oxidative stress induces nuclear loss of DNA repair proteins ku70 and ku80 and apoptosis in pancreatic acinar ar42j cells. *J Biol Chem* **2003**, *278*, 36676-36687.

113. Hanada, K.; Uchida, T.; Tsukamoto, Y.; Watada, M.; Yamaguchi, N.; Yamamoto, K.; Shiota, S.; Moriyama, M.; Graham, D.Y.; Yamaoka, Y. Helicobacter pylori infection introduces DNA double-strand breaks in host cells. *Infect Immun* **2014**, *82*, 4182-4189.