Chapter 20

DNA damage and repair mechanisms in bipolar disorder

Ayşegül Özerdem[1] and Deniz Ceylan[2]
[1]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, United States,
[2]Department of Psychiatry, Faculty of Medicine, Koç University, Istanbul, Turkey

20.1 Introduction

Bipolar disorder (BD) is a chronic, severe and disabling brain disorder, which has disruptive effects on mood regulation, cognitive abilities, and daily functioning (Belmaker, 2004; Ferrari, Baxter, & Whiteford, 2011). BD has also been associated with deleterious effects on general physical health causing increased mortality and morbidity (Grande, Berk, Birmaher, & Vieta, 2016; Perron et al., 2009; Vancampfort et al., 2013). Despite molecular mechanisms underlying BD are largely unknown, a wide range of structural and functional changes, from molecular levels to brain networks, were shown in BD (Benes, 2011; Berk et al., 2011; Maletic & Raison, 2014).

Oxidative stress refers to an imbalance between the production and neutralization of free radicals in favor of production. It is a major cause of DNA damage of various types for various mechanisms. Emerging evidence suggests that multiple biological pathways, such as oxidative stress, hypothalamic–pituitary–adrenal abnormalities, inflammatory dysregulation, mitochondrial dysfunction, are shared between BD and general medical conditions including cardiovascular, metabolic, or inflammatory diseases (Kato, 2019; Maes et al., 2019; Özerdem & Ceylan, 2021; Rosenblat & McIntyre, 2017).

Oxidative stress and related DNA damage are suggested as potential mechanisms underlying the pathophysiology of BD and as contributory mechanisms to the increased medical comorbidity and early aging in BD (Andreazza, 2012; Czarny, Bialek, Ziolkowska, Strycharz, & Sliwinski, 2020; Elvsåshagen et al., 2011; Fries et al., 2017; Özerdem & Ceylan, 2021). Recent data highlight involvement of the DNA repair mechanisms in BD across different states of illness and in response to treatment introducing new potential biomarkers for illness progress and perhaps treatment opportunities (Ceylan et al., 2018a, 2020; Munkholm, Poulsen, Kessing, & Vinberg, 2015).

Biomarkers in Bipolar Disorders. DOI: https://doi.org/10.1016/B978-0-12-821398-8.00005-9

In this chapter, data on oxidative stress and its relevance to DNA damage within the context of BD are presented. DNA damage and its measurement methods are given to provide the reader the context for variability in findings from different studies; various DNA repair mechanisms are introduced and the base excision repair (BER) mechanism is highlighted as the main mechanism to repair the oxidatively induced DNA damage. Data on BER and BD are presented as a source of new potential markers and finally the future directions for new horizons for the underlying mechanisms and future treatment options of BD are outlined.

20.2 Oxidative stress and its relevance to bipolar disorder

Oxidative stress refers to an imbalance between the production and neutralization of free radicals in favor of production. Free radicals are unstable atoms or groups of atoms containing one or more unpaired electron (s) that can be derived from both exogenous sources such as air pollution, smoking, UV light, or generated as byproducts of normal essential metabolic processes, particularly aerobic respiration (Halliwell, 1999). Even in physiological conditions, approximately 5% of the inhaled oxygen is partially reduced in the mitochondrial electron transport chain resulting in the production of free radicals (Harman, 1993). A disturbance in the mitochondrial functioning and energy generation-related pathways, which has repeatedly been associated with the pathophysiology of BD, can ease free radical formation (Kato, 2017, 2019).

Because of their high reactivity due to their unpaired electrons, free radicals tend to engage chemical reactions in order to donate or couple single electrons and reach steady state (Dizdaroglu, Jaruga, Birincioglu, & Rodriguez, 2002). During these chemical reactions, free radicals can lead to chemical changes to molecules, tissues, or organs (Dizdaroglu, 2012). In physiological conditions, free radical load is regularly buffered by antioxidant systems of the body. Antioxidants are enzymatic or nonenzymatic substances that catalyze reactions to neutralize free radicals and metabolize toxic intermediates (Halliwell, 2006). Oxidative stress occurs when the antioxidant systems of the body are overwhelmed by the accumulation of free radicals, and results in damages in various types of macromolecules such as lipids, proteins, and DNA.

A large body of evidence shows the impact of the oxidative stress on the pathogenesis of several medical conditions such as multisystemic diseases and cancers (Dizdaroglu, 2012). Because human brain is particularly vulnerable to oxidative stress due to its raised energy demand, high utilization of oxygen, a large amounts of lipid content as a substrate for oxidation, and poor antioxidant defense; oxidative stress mechanisms were suggested to be involved in the pathophysiology of various types of brain disorders including BD (Watts, Pocock, & Claudianos, 2018). BD has repeatedly been linked to

an increased oxidative stress, which is supported by metaanalysis studies showing higher levels of lipid peroxidation and nitric oxide, as well as increased DNA damage in patients with BD (Andreazza et al., 2008b; Black, Bot, Scheffer, Cuijpers, & Penninx, 2015; Brown, Andreazza, & Young, 2014). BD has also been associated with several mechanisms relevant to oxidative stress, such as mitochondrial dysfunction, which may lead to increased rate of electron leakage, and consequently increased production of free radicals, chronic inflammation, telomere shortening (Colpo et al., 2015; Fries et al., 2017; Kato, 2019). Both clinical and animal studies suggested increased oxidative stress due to manic/depressive symptoms, and decreased oxidative stress levels in remission (Andreazza et al., 2008a; Banerjee, Dasgupta, Rout, & Singh, 2012; Cui, Shao, Young, & Wang, 2007; De Vasconcellos et al., 2006; Wang, Feng, Zhang, & Jiang, 2013). In addition, accumulating evidence suggests that both mood stabilizers and antidepressant agents may exert at least some of their therapeutic effects through their antioxidant actions (Abdel-Wahab & Salama, 2011; Ahmadimanesh et al., 2019; Andreazza, 2008a; Black, Bot, Scheffer, & Penninx, 2017; Shao, Young, & Wang, 2005; Valvassori, 2017). Moreover, a metaanalysis study suggested that antidepressant activity may be mediated by improving oxidative balance and antioxidant functions (Jimenez-Fernandez et al., 2015). Another study suggested that nonresponse to antidepressant treatment may cause elevated levels of oxidative stress markers including DNA oxidation (Lindqvist et al., 2017).

Focusing on oxidative stress markers, previous studies reported consistent and significant alterations in antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidase) in both postmortem brain tissues and a range of biological specimens, such as blood and urine of patients with BD. However, accumulating evidence suggested that stable products of the oxidative processes such as lipid peroxidation or protein/nucleic acid oxidation markers are more likely to distinguish patients and controls than antioxidant enzyme levels. Focusing on stable products, studies showed alterations in markers of lipid peroxidation (e.g., thiobarbituric acid-related substances, malondialdehyde), protein oxidation (e.g., protein carbonyls, 3-nitrotyrosine), and finally oxidation-induced nucleic acid damage (e.g., DNA, RNA, mitochondrial DNA damage) in BD.

20.3 DNA damage and repair mechanisms

DNA is a highly susceptible molecule. Various endogenous and exogenous sources including oxidative insults of environmental, physical, or chemical factors such as ionizing radiation, alkylating and cross-linking agents, as well as free radicals derived from normal metabolism result in a variety of DNA lesions including DNA chain breaks, nucleotide losses, base and sugar

modifications, insertion/deletion mismatches, and DNA−protein cross-links (Halliwell, 2006).

Steady-state levels of DNA damage represent a homeostatic balance between formation and repair. It is estimated that every day each single cell of the human body is subjected to an average of 70,000 DNA lesions (Tubbs & Nussenzweig, 2017). Most of such DNA lesions can be repaired accurately through DNA damage recognition and repair mechanisms. So far, five major endogenous DNA repair pathways that reverse the daily production of DNA damage have been identified: the BER, the nucleotide excision repair (NER), the mismatch repair, homologous recombination, and nonhomologous end-joining (NHEJ) repairs (Dizdaroglu, 2012).

The BER pathway is the most well-defined and studied DNA repair mechanism, which is accountable for repairing small DNA lesions, such as deamination, alkylation, or single-strand breaks, through the activation of several enzymes, to prevent further lesions in DNA. The BER pathway is initiated by one of at least 11 distinct enzymes, the so-called DNA glycosylases. The DNA glycosylases recognize and remove specific damaged bases, generating an abasic site, which is subsequently cleaved by an endonuclease (Fig. 20.1). Finally, the resulting single-stranded break can be processed by the actions of polymerase and ligase enzymes. NER is another important mechanism that repairs UV products, DNA cross-links, and bulky lesions through the action of more than 30 proteins in a stepwise manner that includes damage recognition, unwinding of the helix, dual incision of the lesion, gap filling, and strand ligation. Other DNA repair pathways are the mismatch repair that corrects base mismatches and small insertions or deletions, homologous recombination and NHEJ that repair DNA strand breaks notably induced by ionizing radiation (Chatterjee & Walker, 2017; Dizdaroglu, 2012, 2015).

An imbalance between DNA damage and repair results in the increased DNA damage leading to a destabilization in the cellular metabolic homeostasis and genomic stability, leading to mutagenic processes, early aging, and several medical conditions. Increased oxidative DNA damage has repeatedly been shown in neurological, cardiovascular, metabolic, inflammatory diseases and cancers, as well as psychiatric disorders including BD (Czarny et al., 2020; Dizdaroglu, 2012, 2015).

20.4 DNA damage markers in bipolar disorder

Oxidative DNA damage in BD has been investigated using different specimens such as postmortem brain samples, blood, urine and various types of quantification techniques including immunosorbent assays, chromatographic techniques. Postmortem studies focusing on DNA damage in BD reported either unchanged DNA fragmentation (Benes, Walsh, Bhattacharyya, Sheth, & Berretta, 2003) or increased DNA fragmentation in the anterior cingulate

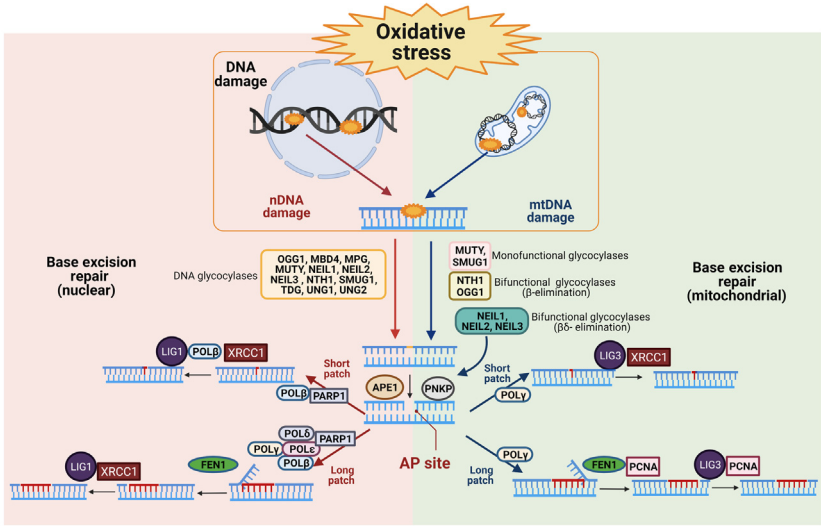

FIGURE 20.1 Oxidatively induced nuclear and mitochondrial DNA damage and the BER pathway: both nuclear and mitochondrial DNA bases are prone to oxidatively induced damage. The illustration shows shared pathways and slight differences between mitochondrial and nuclear BER pathways. In both pathways, oxidatively induced DNA bases are recognized and removed by the concerted activities of DNA glycosylases (e.g., OGG1, NEIL, MUTY) and APE (apurinic/apyrimidinic endodeoxyribonuclease), leaving an AP site. However, the mitochondrial BER initiated by the NEIL glycosylases (NEIL1, NEIL2, and NEIL3) creates a single-nucleotide gap which is removed by PNKP (polynucleotide kinase 3′-phosphatase) instead of APE. Finally, the process can either take the route of long-patch repair or alternatively the short-patch repair pathway. Figure is created using BioRender.

cortex slices (Buttner, Bhattacharyya, Walsh, & Benes, 2007). A further postmortem study presented increased single- and double-strand breaks to DNA in the parietal, temporal and occipital lobes, thalamus, cerebellum, hypothalamus, medulla, pons, and frontal cortex, but not in the hippocampus of patients with BD (Mustak et al., 2010). Another study reported that oxidative nucleic acid damage located predominantly in the cytoplasm, rather than in the cell nucleus, in hippocampal tissues from patients with BD, and thus oxidative stress affects RNA more than DNA (Che, Wang, Shao, & Young, 2010). On the other hand, a more recent postmortem study suggested the DNA as a main target of oxidative stress modifications in the central nervous system in psychiatric disorders (Christensen et al., 2018).

A prior study investigating DNA damage in peripheral samples showed increased frequency of DNA fragmentation in leukocyte samples of patients with BD using the Comet Assay technique, and the frequency of DNA damage correlated with the severity symptoms of depression and mania (Andreazza et al., 2007). Following studies shifted the focus on oxidized DNA adducts in peripheral samples of patients with BD, such as serum,

whole blood, and urine (Black et al., 2015; Brown et al., 2014). For example, a study investigated various types of DNA base lesions using gas chromatography and tandem mass spectroscopy, and modified nucleosides using liquid chromatography−tandem mass spectroscopy, and showed increased levels of 2,6-diamino-4-oxo-5-formamidopyrimidine (Fapy-Gua), 4,6-diamino-5-formamidopyrimidine (Fapy-Ade), and 5-hydroxy-5-methylhydantoin (5-OH-5-MeHyd) in leukocytes of euthymic patients with BD (Ceylan et al., 2018b). However, in most studies focusing on peripheral levels of oxidative damage, DNA damage has been assessed by quantitative measurement of the 8-hydroxy-2′-deoxyguanosine (8-oxo-dG) nucleoside in either blood or urine samples of patients with BD (Black et al., 2015).

The 8-oxo-dG is a DNA lesion formed by the oxidation of guanine residues. Because guanine has a lower one-electron reduction potential than the other nucleosides in DNA, the 8-oxo-dG is the most common oxidative lesion observed in DNA where up to 100,000 lesions are estimated to be formed in DNA per cell daily (Hübscher & Maga, 2011; Kawanishi, Hiraku, & Oikawa, 2001). Therefore despite a plethora of identified products of DNA oxidation, the 8-oxo-dG is the most extensively studied oxidative DNA lesion in medical research as a marker of oxidative DNA damage. Up to date, three metaanalysis studies suggested increased levels of 8-oxo-dG in BD (Andreazza et al., 2008b; Black et al., 2015; Brown et al., 2014). However, there is a prominent variance in the studies with respect to techniques used in quantification of the 8-oxo-dG (e.g., ELISA, chromatographic techniques), source of DNA (e.g., urine, blood, cell culture) and characteristics of study populations (e.g., euthymic, symptomatic, rapid cycling) (Black et al., 2015; Czarny et al., 2020; Özerdem & Ceylan, 2021).

20.5 Quantification of 8-oxo-dG in bipolar disorder

A metaanalysis study pooling data of 8-oxo-dG levels in affective disorders revealed a variability in findings and connected this variability to the use of different biological specimens and laboratory techniques among the studies (Black et al., 2015). While urinary 8-oxo-dG levels originate from tissue DNA, urine 8-oxo-dG levels present global excretion of 8-oxo-dG from the whole body, and consequently is a more valid indicator of systemic oxidative stress. However, approximately half of the studies investigated 8-oxo-dG levels in blood samples of patients with BD, although blood levels of 8-oxo-dG may change suddenly due to the continuous DNA repair processes, and consequently blood and tissue samples may present a snapshot reflecting the balance between damage and repair rate. Despite possible impacts of continuing DNA repair processes on the findings requires further consideration, only a few studies investigated DNA damage together with repair, indicating a dynamic relationship between damage and repair processes (Ceylan et al., 2018b; Munkholm, Peijs, Vinberg, & Kessing, 2015). On the other hand,

recent data present strong correlations among 8-oxo-dG levels in cerebrospinal fluid and urine samples (Christensen et al., 2018; Knorr et al., 2019), and in plasma and urine samples suggesting positive relation between steady-state DNA damage and systemic DNA damage (Wang et al., 2016), as well as both sides of the blood−brain barrier (Christensen et al., 2018).

Prior studies quantified 8-oxo-dG levels in total blood-derived DNA samples using ELISA technique. For example, a study by Soeiro-de-Souza et al. (2013) presented a significant increase in 8-oxo-dG levels, which correlated with cumulative number of previous manic episodes, in a medication free group of symptomatic patients with BD compared to healthy controls (Soeiro-de-Souza et al., 2013). A following study that used similar quantification techniques suggested influences of smoking, sex and illness states on the blood levels of 8-oxo-dG (Ceylan et al., 2018a). Huzayyin et al. (2014) showed unchanged levels of 8-oxo-dG in lymphoblast cell culture derived from lymphocytes of an excellent lithium responder subgroup of euthymic patients with BD using ELISA (Huzayyin et al., 2014). Urine 8-oxo-dG in BD was quantified in three studies using liquid chromatography and mass spectroscopy. A cohort study including 37 rapid cycling BD patients and 40 controls presented increased levels of 8-oxo-dG even when adjusted to demographical, lifestyle, and metabolic factors (Munkholm, Poulsen, et al., 2015). Another study, by the same research group, consisting of 54 patients with BD and 35 healthy controls showed significantly increased urine 8-oxo-dG levels in both euthymic and active states of BD in comparison to healthy controls, however the difference was not significant the after adjustment for body mass index, alcohol use, smoking, sex, and age (Jacoby, Vinberg, Poulsen, Kessing, & Munkholm, 2016). More recently, a study consisting of 24 patients with bipolar depression, 33 patients wit unipolar depression and 61 healthy controls showed higher levels of 8-oxo-dG in acutely depressed patients in comparison to healthy controls even after adjusting for several confounders (e.g., age, sex, smoking, lifestyle factors) (Ceylan et al., 2020).

20.6 DNA damage and affective states of bipolar disorder

A number of studies consistently showed unchanged 8-oxo-dG levels in euthymic patients with BD compared to healthy controls, despite using different biological specimens such as blood and urine and different laboratory techniques such as ELISA (Ceylan et al., 2018a; Huzayyin et al., 2014) or chromatographic techniques (Ceylan et al., 2018b; Jacoby et al., 2016). For example, Ceylan et al. (2018a,b) suggested that levels of 8-oxo-dG are affected by illness episodes, but present no change in euthymia (Ceylan et al., 2018a). A lymphoblast cell culture study showed unchanged levels of 8-oxo-dG in an excellent lithium responder subgroup of euthymic patients with BD (Huzayyin et al., 2014). Another study confirmed unchanged levels of 8-oxo-dG in euthymia, despite use of a highly sensitive technique, gas

chromatography-tandem mass spectroscopy, in leukocyte-derived DNA samples of 32 patients with BD (Ceylan et al., 2018b). Consistently, using a modified ultraperformance liquid chromatography and mass spectrometry assay, Jacoby et al. (2016) indicated unchanged levels of 8-oxo-dG in urine-derived DNA samples of euthymic patients with BD after adjustments for lifestyle and demographic factors (Jacoby et al., 2016). On the other hand, a longitudinal cohort study of 37 rapid cycling patients with BD demonstrated significantly elevated urine levels of 8-oxo-dG both in affective and euthymic states (Munkholm, Poulsen, et al., 2015). Of note, this study included a rapid cycling group of patients with BD, which is a special subgroup associated with a more severe clinical course and poorer outcomes.

Emerging evidence suggests increased levels of 8-oxo-dG in urine (Munkholm, Poulsen, et al., 2015) and whole blood DNA (Ceylan et al., 2018a; Soeiro-de-Souza et al., 2013) in manic and depressive episodes in comparison to healthy controls. Two studies measured levels of 8-oxo-dG in whole blood-derived DNA samples using ELISA technique. The first one suggested significantly increased levels of 8-oxo-dG in a sample consisting of 50 symptomatic and drug free patients with BD (26 in mania and 24 in depression) in comparison to healthy controls (Soeiro-de-Souza et al., 2013). The second study, including 75 patients (37 in euthymia, 18 in mania, 20 in depression) and 60 healthy control subjects indicated a trend of increase in illness episodes, but no difference between mania and depression (Ceylan et al., 2018a).

Follow-up studies, using chromatographic techniques, investigated the potential impacts of illness episodes on the levels of 8-oxo-dG (Ceylan et al., 2020; Jacoby et al., 2016; Knorr et al., 2019). Repeated measurements in various affective phases revealed significant increases in manic/hypomanic states in comparison to euthymia, and decreased levels of 8-oxo-dG from a manic or mixed episode to remission even above-mentioned adjustments (Jacoby et al., 2016). A naturalistic, prospective study reported the results of a follow-up of newly diagnosed euthymic patients with BD for 1 year after the baseline assessment of cerebrospinal fluid and urinary 8-oxo-dG as well as 8-oxo-Gua, an RNA damage marker (Knorr et al., 2019). Measurements were repeated in case of a new episode occurrence, after remitting from that episode and at the end of 1 year while in remission. RNA damage was significantly higher in the patients at baseline, and showed increases with a new episode and over time during follow-up indicating a state and trend dependence, whereas the DNA damage marker showed only state-dependent changes in patients. Both markers remained stable over time in controls, and urine and cerebrospinal fluid levels of both markers were correlated (Knorr et al., 2019).

Consistently, a recent study presented significant decreases in urine 8-oxo-dG levels after remission of depressive episodes in a cohort consisting of 37 unipolar, 23 bipolar depression patients (Ceylan et al., 2020). The 8-oxo-dG

levels significantly decreased after resolution of depressive symptoms after 2 months suggesting a causal relationship between depressive episodes and increased 8-oxo-dG levels. However, 8-oxo-dG levels differed between unipolar or bipolar depression in neither acute phase nor remission, suggesting that increases may be related to the biological load of affective episodes rather than the BD diagnosis. Furthermore, 8-oxo-dG was offered as a component of a multisystem composite biomarker for BD, but the composite scores showed low discrimination between euthymia and affective states (Munkholm, Peijs, et al., 2015).

On the contrary with the emerging evidence supporting impacts of affective states on the levels of 8-oxo-dG, one study reported unchanged serum levels of 8-oxo-dG in patients with manic episodes in comparison to healthy controls and remitted phase of BD (Tsai & Huang, 2015). However, it must be noted that the follow-up group was relatively small, that is 23 patients, which could have affected the results. In addition, rapid cycling patients with BD presented increased urine levels of 8-oxo-dG through mania, depression, and euthymic phases with no significant difference among the affective states. However, authors noted that the small number of samples obtained in a manic or mixed state, and relatively mild severity of symptoms might have contributed to the lack of statistical significance (type II error) in comparisons among the affective states (Munkholm, Peijs, et al., 2015).

In summary, accumulated findings indicate that increased oxidative DNA damage, implicated by 8-oxo-dG, is present in BD in particularly acute illness episodes, however, it is still unclear whether this change has trait-specific properties. There are contradicting findings with regard to 8-oxo-dG levels in euthymic patients, which may be caused by the methodological heterogeneity across studies in terms of patient population, sampling, measurement techniques, and treatment.

20.7 DNA repair markers in bipolar disorder

DNA repair mechanisms, particularly the BER pathway, have recently gained attention in BD. Even only a few studies addressed the DNA repair pathways in BD (Ceylan et al., 2018b, 2019, 2020; Munkholm, Peijs, et al., 2015), there is some evidence that not only increases in oxidative load but also impairments in DNA repair pathways may contribute to the increased DNA damage in psychiatric disorders such as schizophrenia (Muraleedharan, Menon, Rajkumar, & Chand, 2015; Odemis et al., 2016; Topak, Ozdel, Dodurga, & Secme, 2018), and unipolar depression (Czarny et al., 2020). For example, studies using Comet Assay suggested significant decreases in the efficacy of DNA repair after exposure to oxidative damage in depression (Czarny et al., 2015b, 2017) and schizophrenia (Muraleedharan et al., 2015; Topak et al., 2018). Further studies exhibited certain single nucleotide polymorphisms of BER genes in depression (Czarny et al., 2015a, 2016, 2017, 2018), as well as

in schizophrenia (Muraleedharan et al., 2015; Odemis et al., 2016; Topak et al., 2018).

Above all repair pathways, BER is particularly responsible for excision of oxidation-induced DNA lesions. The BER mechanism is initiated by a set of enzymes, the so-called DNA glycosylases, which are specifically responsible for the recognition, removal of certain DNA adducts in the initial step of the BER. For example, the 8-oxoguanine DNA glycosylase 1 (OGG1) is a BER enzyme specialized for excision of 8-oxo-dG lesions, which is the most widely studied DNA lesion in BD. On the other hand, NEI such as DNA glycosylases (NEIL1,2) recognize oxidized pyrimidines, formamidopyrimidine, and thymine residues. After the actions of DNA glycosylases, downstream BER enzymes restore the correct nucleotide. First, an abasic (apurinic/apyrimidinic) site is generated by the apurinic/apyrimidinic endonuclease-1 (APEX-1) creating a strand break. Second, DNA polymerases, such as poly (ADP-ribose) polymerase 1 (PARP1), polymerase gamma (POLG; mitochondrial DNA polymerase), delta (PolD) and epsilon (PolE), add an appropriate base, and finally the strand is ligated by DNA ligases (LIG1, LIG3) (Chatterjee & Walker, 2017).

Only two studies investigated the expressions of the BER genes in peripheral samples of patients with BD, whereas several studies reported significant alterations in expression levels of genes encoding the BER enzymes in depressive disorders (Forlenza & Miller, 2006; Irie, Asami, Ikeda, & Kasai, 2003; Irie, Asami, Nagata, Miyata, & Kasai, 2002; Irie, Tamae, Iwamoto-Tanaka, & Kasai, 2005; Lindqvist et al., 2017; Maes et al., 2009; Wei et al., 2009a,b). One of these studies quantified relative expressions of two BER genes, OGG1 and NEIL1, reported that euthymic patients with BD had significantly lower levels of OGG1 expressions compared to controls, while no significant difference was found for the levels of *NEIL1* expressions (Ceylan et al., 2018b). Other study measured relative expressions of two BER genes, *OGG1* and POLG, in a group of rapid cycling patients with BD during a 6−12 month period across different states of illness (i.e., mania/hypomania, mixed, depression, and euthymia) in comparison with healthy controls, and suggested significant downregulations in OGG1 and POLG expressions, regardless of illness episodes, in BD group in comparison to healthy controls (Munkholm, Peijs, et al., 2015).

As guanine nucleotides constitute the primary target of oxidation due to their low oxidation potential in comparison to other nucleic acid bases (Kawanishi et al., 2001), OGG1 enzyme, which is specialized for excision of guanine lesions such as 8-oxo-dG and Fapy-Gua, has received most attention in the BER pathway. Expression levels of *OGG1* gene have been shown to be dysregulated in several medical diseases and cancers (Dizdaroglu, 2015), and some studies of depression in cancer presented overexpression of OGG1 (Wei et al., 2009a; Zhou et al., 2007). Dysregulation of OGG1 has been shown in major depressive disorder (Forlenza & Miller, 2006; Irie et al.,

2002, 2003, 2005; Lindqvist et al., 2017; Maes et al., 2009), as well as in BD (Ceylan et al., 2018b; Munkholm, Peijs, et al., 2015). A further study compared 8-oxo-dG levels along with plasma levels of OGG1 protein in 48 patients with type I BD either in euthymic ($n = 28$) or manic ($n = 20$) states (43 medicated) in comparison to 49 healthy controls using ELISA technique (Ceylan et al., 2019). The authors reported significantly higher plasma levels of OGG1 protein in both euthymic and manic patients in comparison to healthy controls, and this difference was mainly driven by female subjects (Ceylan et al., 2019). More recently, Ceylan et al. (2020) investigated the alterations of 8-oxo-dG levels along with *OGG1* gene expression levels between depressive episode and remission in a cohort consisting of 37 unipolar, 23 bipolar depression patients, and 61 healthy controls (Ceylan et al., 2020). The findings of the study suggested increased levels of 8-oxo-dG and a downregulation of OGG1 gene expression in acute depression in both unipolar and BD, in comparison to healthy controls. In addition, the 8-oxo-dG levels were shown to decrease whereas OGG1 gene expressions were shown to increase after resolution of depressive symptoms after 2 months, suggesting a dynamic relationship between illness episodes and DNA damage and repair mechanisms (Ceylan et al., 2020).

The BER enzymes, other than OGG1, are less studied, and they require further attention. Our group have recently shown genes encoding for BER enzymes *NEIL1, APE1, XRCC1*, and POLε to be hypomethylated, and *MPG, MUTYH* hypermethylated in the temporopolar region (BA38) in postmortem gray matter tissues of patients with BD ($n = 20$) compared to sex- and age-matched controls ($n = 10$) (Ozerdem et al., 2019). On the other hand, polymorphisms of Poly (ADP-ribose) polymerase PARP, a nuclear DNA-binding protein, which can detect DNA strand breaks in BER have been associated with Alzheimer's disease (Sliwinska et al., 2017) and depression (Czarny et al., 2017). Increased expression levels of PARP1 and OGG1, were shown in oligodendrocytes laser captured from Brodmann area 10 (BA10) and/or amygdala (uncinate fasciculus) and astrocyte slices of 10 patients with depression and 13 controls (Szebeni et al., 2016). Another study showed increased expression levels of PARP1 in peripheral blood samples of patients with depression (Ahmadimanesh et al., 2019). Interestingly, a recent case report presented a rapid improvement of anxiety and depression symptoms following administration of a PARP1 inhibitor agent (i.e., niraparib), and a rapid reversal of improvement after discontinuation of niraparib, suggesting a possible involvement of PARP1 in psychiatric disorders (Jewett et al., 2020). In addition, minocycline, a potent PARP1 inhibitor (Alano, Kauppinen, Valls, & Swanson, 2006), shows antidepressant effects (Rosenblat & McIntyre, 2018). Animal studies also present antidepressant-like effects of PARP1 inhibition (Ordway et al., 2017; Sriram et al., 2015). Preclinical studies suggest that PARP signaling may be modulated by lithium and sertraline (Chinnapaka, Bakthavachalam, & Munirathinam, 2020; Greenblatt, Ndiaye, Chen, & Kunnimalaiyaan, 2010).

In addition, PARP1 knockout mice exhibited a range of psychiatric symptoms such as anxiety, depression, social interaction deficits, cognitive impairments, and prepulse inhibition deficits, besides reduced brain weight with enlarged ventricle as well as decreased adult neurogenesis in the hippocampus (Hong et al., 2019). In support of these data, future studies investigating expressions of PARP1 in BD are needed. A study investigated the effect of the X-ray repair cross-complementation group 1 (XRCC1) Arg194Trp and Arg399Gln polymorphisms on the illness risk in 228 individuals with BD and 236 controls. Results showed significantly higher frequency of the haplotype "194Trp-399Gln" among BD patients compared to controls. As the haplotype "194Trp-399Gln" in the general population is very low, the finding merits further investigation to understand the role of XRCC1 polymorphism in the development of BD (Saadat, Mohammadynejad, Ghanizadeh, & Saadat, 2012). A microarray analysis of gene expressions of depressed ($n = 52$) and nondepressed ($n = 30$) patients with colorectal carcinoma and healthy controls ($n = 30$) showed that the group with depression had significantly lower levels of XRCC1, XRCC3, LIG1, MPG, MUTYH, and NTH1, significantly higher levels of UNG and downregulation of XRCC3 (Wei et al., 2009a).

20.8 Future directions

20.8.1 Mitochondrial DNA damage and repair and bipolar disorder

Up to this point, the DNA damage that has been discussed is the damage to the nuclear DNA. However, compiling data points at DNA damage in the mitochondria in BD. Early findings from Kato, Stine, McMahon, and Crowe (1997) led to the theory of mitochondrial DNA (mtDNA) damage in the pathology of BD (Kato et al., 1997). More recent studies presented contradictory findings on the mtDNA content and deletions, some showing unchanged (Fuke, Kametani, & Kato, 2008; Kakiuchi et al., 2005; Mamdani, Rollins, Morgan, Sequeira, & Vawter, 2014; Sabunciyan et al., 2007; Tervasmäki et al., 2018; Torrell et al., 2013), some others significantly increased mtDNA deletion (Sequeira et al., 2012; Shao et al., 2008) in various parts of postmortem brain tissue samples of patients with BD. A more recent study demonstrated a brain region-dependent effect on the levels of mtDNA content in patients with BD and SCZ (Bodenstein et al., 2019). Circulating cell-free mitochondrial DNA (ccf-mtDNA) was shown to be potentially associated with depression symptoms in adolescent BD (Jeong et al., 2020). Beyond their primary role in energy generation, mitochondria have critical roles in cellular signaling, fatty acid oxidation, calcium signaling, apoptosis, cell-cycle regulation, and immune responses (Kowaltowski, 2000; Shaughnessy et al., 2015; Stehling & Lill, 2013).

Mitochondrial dysfunction and associated diseases can result from mutations and damage directly related with mitochondrial genes as well as damaged nuclear proteins that translocate to the mitochondria can result in several diseases such as type II diabetes, Leigh syndrome, ataxia, renal dysfunction, and cardiovascular diseases and cancer (Prakash & Doublié, 2015).

Just like nuclear DNA, mtDNA is damaged by genotoxic assaults from such exogenous sources as exposure to chemotherapeutic drugs as well as from endogenous sources including reactive oxygen species (ROS) that form as byproducts of mitochondrial respiration (Yakes & Van Houten, 1997). Evidence suggests that mtDNA molecules are more susceptible to oxidized DNA damage than nuclear DNA due to their proximity to sites of oxidative phosphorylation (Shaughnessy et al., 2015; Yakes & Van Houten, 1997). The BER pathway has been established as the primary repair pathway in the mitochondrion. DNA glycosylases, which carry out the initiation step of BER are monofunctional or bifunctional based on their possession of associated intrinsic lyase activity. The DNA glycosylases are encoded by nuclear genes and some of them translocate to the mitochondria through a mitochondrial targeting signal containing a mitochondrial targeting signal that allows for translocation to the mitochondria (Larsen, Rasmussen, & Rasmussen, 2005; Takao, Aburatani, Kobayashi, & Yasui, 1998). For example, polymerase β (POLB) functions in incorporating the correct nucleotide into the DNA in the nucleus. However, POLG is transported to the mitochondrion, for the same function. DNA ligase I is the responsible enzyme for ligation in the nucleus whereas ligase III performs the same function in the mitochondria BER in the mitochondria (Prakash & Doublié, 2015).

Despite current knowledge on the crosstalk between nucleus and mitochondria within the context of DNA glycosylases, the crosstalk between the nucleus and mitochondria in mediating repair in the mitochondria remains to be elucidated. Within this context, DNA damage and repair in BD as a mechanism of illness become even further pronounced as a new trajectory for new treatment discoveries.

20.8.2 Cancer research and bipolar disorder

Recent years witnessed a series of studies testing lithium as a new horizon in cancer treatment via DNA damage and repair mechanisms. Pyruvate salt of lithium was shown to reduce oxidative DNA damage in the blood of BD patients in vitro (Valentina, Ekaterina, Nikolay, & Evgenii, 2020). In rats, pretreatment with lithium prevented hyperlocomotion and brain oxidative damage in ketamine-induced mania (Recart et al., 2021). Lithium is considered an active homeostatic regulator as its neurotrophic and neuroprotective effects are mostly evident in the presence of pathology (Machado-Vieira, 2018). Data show that lithium promotes DNA stability and survival of ischemic retinal neurocytes by upregulating DNA ligase IV which exists in nuclei

and plays a role in repair of double-strand breaks by NHEJ and V(D)J recombination (Yang et al., 2016). LiCl at 3 mM dose was shown to increase neural stem/progenitor cells in S phase, boost neurosphere growth and reduce DNA damage in vitro after irradiation (Zanni et al., 2015). Lithium treatment was shown to reverse irradiation-induced loss of hippocampal neurogenesis and cognitive impairment even when introduced long after the injury (Zanni et al., 2021). Lithium chloride was shown to induce intrinsic apoptosis in Human choroidal melanoma cells via cleavage of PARP together with caspase 8, caspase 9, caspase 3. The finding was found contributory to potential cancer treatments involving LiCl (Zhang, Zhang, Li, Zhao, & Zhang, 2021). Future findings about the modulatory effects on DNA damage and repair of lithium may aid discovery of new treatments with BD.

References

Abdel-Wahab, B. A., & Salama, R. H. (2011). Venlafaxine protects against stress-induced oxidative DNA damage in hippocampus during antidepressant testing in mice. *Pharmacology, Biochemistry, and Behavior*, *100*, 59–65. Available from https://doi.org/10.1016/j.pbb.2011.07.015.

Ahmadimanesh, M., Abbaszadegan, M. R., Morshedi, R. D., Moallem, S. A., Mohammadpour, A. H., & Etemad, L. (2019). Effects of selective serotonin reuptake inhibitors on DNA damage in patients with depression. *Journal of Psychopharmacology (Oxford, England)*, *026988111987446*. Available from https://doi.org/10.1177/0269881119874461.

Alano, C. C., Kauppinen, T. M., Valls, A. V., & Swanson, R. A. (2006). Minocycline inhibits poly(ADP-ribose) polymerase-1 at nanomolar concentrations. *Proceedings of the National Academy of Sciences (USA)*, *103*, 9685–9690. Available from https://doi.org/10.1073/pnas.0600554103.

Andreazza, A. C. (2012). Combining redox-proteomics and epigenomics to explain the involvement of oxidative stress in psychiatric disorders. *Molecular Biosystems*, *8*, 2503–2512. Available from https://doi.org/10.1039/c2mb25118c.

Andreazza, A. C., Kauer-Sant'Anna, M., Frey, B. N., Stertz, L., Zanotto, C., Ribeiro, L., … Kapczinski, F. (2008a). Effects of mood stabilizers on DNA damage in an animal model of mania. *Journal of Psychiatry & Neuroscience*, *33*, 516–524.

Andreazza, A. C., Kauer-Sant'Anna, M., Frey, B. N., Bond, D. J., Kapczinski, F., Young, L. T., & Yatham, L. N. (2008b). Oxidative stress markers in BD: A *meta*-analysis. *Journal of Affective Disorders*, *111*, 135–144. Available from https://doi.org/10.1016/j.jad.2008.04.013.

Andreazza, A. C., Noronha Frey, B., Erdtmann, B., Salvador, M., Rombaldi, F., Santin, A., … Kapczinski, F. (2007). DNA damage in BD. *Psychiatry Research*, *153*, 27–32. Available from https://doi.org/10.1016/j.psychres.2006.03.025.

Banerjee, U., Dasgupta, A., Rout, J. K., & Singh, O. P. (2012). Effects of lithium therapy on Na + -K + -ATPase activity and lipid peroxidation in BD. *Progress in Neuro-Psychopharmacology & and Biological Psychiatry*, *37*, 56–61. Available from https://doi.org/10.1016/j.pnpbp.2011.12.006.

Belmaker, R. H. (2004). Bipolar disorder. *New England Journal of Medicine*, *351*, 476–486. Available from https://doi.org/10.1056/NEJMra035354.

Benes, F. M. (2011). The neurobiology of BD: From circuits to cells to molecular regulation. *Current Topics in Behavoral Neurosciences.*, *5*, 127–138.

Benes, F. M., Walsh, J., Bhattacharyya, S., Sheth, A., & Berretta, S. (2003). DNA fragmentation decreased in schizophrenia but not BD. *Archives of General Psychiatry*, *60*, 359–364.

Berk, M., Kapczinski, F., Andreazza, A. C., Dean, O. M., Giorlando, F., Maes, M., … Malhi, G. S. (2011). Pathways underlying neuroprogression in BD: Focus on inflammation, oxidative stress and neurotrophic factors. *Neuroscience and Biobehavioral Reviews*, *35*, 804–817. Available from https://doi.org/10.1016/j.neubiorev.2010.10.001.

Black, C. N., Bot, M., Scheffer, P. G., & Penninx, B. W. J. H. (2017). Oxidative stress in major depressive and anxiety disorders, and the association with antidepressant use; results from a large adult cohort. *Psychological Medicine*, *47*, 936–948. Available from https://doi.org/10.1017/S0033291716002828.

Black, C. N., Bot, M., Scheffer, P. G., Cuijpers, P., & Penninx, B. W. J. H. (2015). Is depression associated with increased oxidative stress? A systematic review and *meta*-analysis. *Psychoneuroendocrinology*, *51*, 164–175. Available from https://doi.org/10.1016/j.psyneuen.2014.09.025.

Bodenstein, D. F., Kim, H. K., Brown, N. C., Navaid, B., Young, L. T., & Andreazza, A. C. (2019). Mitochondrial DNA content and oxidation in BD and its role across brain regions. *NPJ Schizophrenia*, *5*, 1–8. Available from https://doi.org/10.1038/s41537-019-0089-5.

Brown, N. C., Andreazza, A. C., & Young, L. T. (2014). An updated *meta*-analysis of oxidative stress markers in BD. *Psychiatry Research*, *218*, 61–68. Available from https://doi.org/10.1016/j.psychres.2014.04.005.

Buttner, N., Bhattacharyya, S., Walsh, J., & Benes, F. M. (2007). DNA fragmentation is increased in non-GABAergic neurons in BD but not in schizophrenia. *Schizophrenia Research*, *93*, 33–41. Available from https://doi.org/10.1016/j.schres.2007.01.030.

Ceylan, D., Scola, G., Tunca, Z., Isaacs-Trepanier, C., Can, G., Andreazza, A. C. A. C., … Özerdem, A. (2018a). DNA redox modulations and global DNA methylation in BD: Effects of sex, smoking and illness state. *Psychiatry Research*, *261*, 589–596. Available from https://doi.org/10.1016/j.psychres.2017.12.051.

Ceylan, D., Tuna, G., Kirkali, G., Tunca, Z., Can, G., Arat, H. E., … Özerdem, A. (2018b). Oxidatively-induced DNA damage and base excision repair in euthymic patients with BD. *DNA Repair*, *65*, 64–72. Available from https://doi.org/10.1016/j.dnarep.2018.03.006.

Ceylan, D., Yılmaz, S., Bora, U., Tuna, G., Ildız, A., Akan, P., … Özerdem, A. (2019). Increased plasma levels of 8-oxoguanine DNA glycosylase-1 in BD. *Psychiatry and Clinical Neurosciences*, *73*, 719–720. Available from https://doi.org/10.1111/pcn.12928.

Ceylan, D., Yılmaz, S., Tuna, G., Kant, M., Er, A., Ildız, A., … Özerdem, A. (2020). Alterations in levels of 8-Oxo-2'-deoxyguanosine and 8-oxoguanine DNA glycosylase 1 during a current episode and after remission in unipolar and bipolar depression. *Psychoneuroendocrinology*, *114*. Available from https://doi.org/10.1016/j.psyneuen.2020.104600.

Chatterjee, N., & Walker, G. C. (2017). Mechanisms of DNA damage, repair, and mutagenesis. *Environmental and Molecular Mutagenesis*, *58*, 235–263. Available from https://doi.org/10.1002/em.22087.

Che, Y., Wang, J.-F., Shao, L., & Young, T. (2010). Oxidative damage to RNA but not DNA in the hippocampus of patients with major mental illness. *Journal of Psychiatry & Neuroscience*, *35*, 296–302. Available from https://doi.org/10.1503/jpn.090083.

Chinnapaka, S., Bakthavachalam, V., & Munirathinam, G. (2020). Repurposing antidepressant sertraline as a pharmacological drug to target prostate cancer stem cells: Dual activation of

apoptosis and autophagy signaling by deregulating redox balance. *American Journal of Cancer Research*, *10*, 2043–2065.

Christensen, M. R., Poulsen, H. E., Henriksen, T., Weimann, A., Ellervik, C., Lynnerup, N., … Banner, J. (2018). Elevated levels of 8-oxoGuo and 8-oxodG in individuals with severe mental illness—An autopsy-based study. *Free Radical Biology & Medicine*, *126*, 372–378. Available from https://doi.org/10.1016/j.freeradbiomed.2018.08.029.

Colpo, G. D., Leffa, D. D., Köhler, C. A., Kapczinski, F., Quevedo, J., & Carvalho, A. F. (2015). Is BD associated with accelerating aging? A *meta*-analysis of telomere length studies. *Journal of Affective Disorders*, *186*, 241–248. Available from https://doi.org/10.1016/j.jad.2015.06.034.

Cui, J., Shao, L., Young, L. T., & Wang, J.-F. (2007). Role of glutathione in neuroprotective effects of mood stabilizing drugs lithium and valproate. *Neuroscience*, *144*, 1447–1453. Available from https://doi.org/10.1016/j.neuroscience.2006.11.010.

Czarny, P., Bialek, K., Ziolkowska, S., Strycharz, J., & Sliwinski, T. (2020). DNA damage and repair in neuropsychiatric disorders. What do we know and what are the future perspectives? *Mutagenesis*, *35*, 79–106.

Czarny, P., Kwiatkowski, D., Galecki, P., Talarowska, M., Orzechowska, A., Bobinska, K., … Sliwinski, T. (2015a). Association between single nucleotide polymorphisms of MUTYH, hOGG1 and NEIL1 genes, and depression. *Journal of Affective Disorders*, *184*, 90–96. Available from https://doi.org/10.1016/j.jad.2015.05.044.

Czarny, P., Kwiatkowski, D., Kacperska, D., Kawczyńska, D., Talarowska, M., Orzechowska, A., … Śliwiński, T. (2015b). Elevated level of DNA damage and impaired repair of oxidative DNA damage in patients with recurrent depressive disorder. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, *21*, 412–418. Available from https://doi.org/10.12659/MSM.892317.

Czarny, P., Kwiatkowski, D., Toma, M., Gałecki, P., Orzechowska, A., Bobińska, K., … Śliwiński, T. (2016). Single-nucleotide polymorphisms of genes involved in repair of oxidative DNA damage and the risk of recurrent depressive disorder. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, *22*, 4455–4474. Available from https://doi.org/10.12659/MSM.898091.

Czarny, P., Kwiatkowski, D., Toma, M., Kubiak, J., Sliwinska, A., Talarowska, M., … Sliwinski, T. (2017). Impact of single nucleotide polymorphisms of base excision repair genes on DNA damage and efficiency of DNA repair in recurrent depression disorder. *Molecular Neurobiology*, *54*, 4150–4159. Available from https://doi.org/10.1007/s12035-016-9971-6.

Czarny, P., Wigner, P., Strycharz, J., Watala, C., Swiderska, E., Synowiec, E., … Sliwinski, T. (2018). Single-nucleotide polymorphisms of uracil-processing genes affect the occurrence and the onset of recurrent depressive disorder. *PeerJ*, *6*, e5116. Available from https://doi.org/10.7717/peerj.5116.

De Vasconcellos, A. P. S., Nieto, F. B., Crema, L. M., Diehl, L. A., De Almeida, L. M., Prediger, M. E., … Dalmaz, C. (2006). Chronic lithium treatment has antioxidant properties but does not prevent oxidative damage induced by chronic variate stress. *Neurochemical Research*, *31*, 1141–1151. Available from https://doi.org/10.1007/s11064-006-9139-2.

Dizdaroglu, M. (2012). Oxidatively induced DNA damage: Mechanisms, repair and disease. *Cancer Letters*, *327*, 26–47. Available from https://doi.org/10.1016/j.canlet.2012.01.016.

Dizdaroglu, M. (2015). Oxidatively induced DNA damage and its repair in cancer. *Mutation Research/Reviews in Mutation Research.*, *763*, 212–245. Available from https://doi.org/10.1016/j.mrrev.2014.11.002.

Dizdaroglu, M., Jaruga, P., Birincioglu, M., & Rodriguez, H. (2002). Free radical-induced damage to DNA: Mechanisms and measurement. *Free Radical Biology & Medicine*, *32*, 1102–1115.

Elvsåshagen, T., Vera, E., Bøen, E., Bratlie, J., Andreassen, O. A., Josefsen, D., … Boye, B. (2011). The load of short telomeres is increased and associated with lifetime number of depressive episodes in bipolar II disorder. *Journal of Affective Disorders*, *135*, 43–50. Available from https://doi.org/10.1016/j.jad.2011.08.006.

Ferrari, A. J., Baxter, A. J., & Whiteford, H. A. (2011). A systematic review of the global distribution and availability of prevalence data for BD. *Journal of Affective Disorders*, *134*, 1–13. Available from https://doi.org/10.1016/j.jad.2010.11.007.

Forlenza, M. J., & Miller, G. E. (2006). Increased serum levels of 8-hydroxy-2′-deoxyguanosine in clinical depression. *Psychosomatic Medicine*, *68*, 1–7. Available from https://doi.org/10.1097/01.psy.0000195780.37277.2a.

Fries, G. R., Bauer, I. E., Scaini, G., Wu, M.-J., Kazimi, I. F., Valvassori, S. S., … Quevedo, J. (2017). Accelerated epigenetic aging and mitochondrial DNA copy number in BD. *Translational Psychiatry*, *7*, 1283. Available from https://doi.org/10.1038/s41398-017-0048-8.

Fuke, S., Kametani, M., & Kato, T. (2008). Quantitative analysis of the 4977-bp common deletion of mitochondrial DNA in postmortem frontal cortex from patients with BD and schizophrenia. *Neuroscience Letters*, *439*, 173–177. Available from https://doi.org/10.1016/j.neulet.2008.05.009.

Grande, I., Berk, M., Birmaher, B., & Vieta, E. (2016). Bipolar disorder. *The Lancet*, *387*, 1561–1572. Available from https://doi.org/10.1016/S0140-6736(15)00241-X.

Greenblatt, D. Y., Ndiaye, M., Chen, H., & Kunnimalaiyaan, M. (2010). Lithium inhibits carcinoid cell growth in vitro. *American Journal of Translational Research*, *2*, 248–253.

Halliwell, B. (1999). Oxygen and nitrogen are pro-carcinogens. Damage to DNA by reactive oxygen, chlorine and nitrogen species: Measurement, mechanism and the effects of nutrition. *Mutation Research - Genetic Toxicology and Environmental Mutagenesis*, *443*, 37–52. Available from https://doi.org/10.1016/S1383-5742(99)00009-5.

Halliwell, B. (2006). Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. *Plant Physiology*, *141*, 312–322. Available from https://doi.org/10.1104/pp.106.077073.

Harman, D. (1993). Free radical involvement in aging: Pathophysiology and therapeutic implications. *Drugs & Aging*, *3*, 60–80. Available from https://doi.org/10.2165/00002512-199303010-00006.

Hong, S., Yi, J. H., Lee, S., Park, C. H., Ryu, J. H., Shin, K. S., & Kang, S. J. (2019). Defective neurogenesis and schizophrenia-like behavior in PARP-1-deficient mice. *Cell Death and Disease*, *10*. Available from https://doi.org/10.1038/s41419-019-2174-0.

Hübscher, U., & Maga, G. (2011). DNA replication and repair bypass machines. *Current Opinion in Chemical Biology*, *15*, 627–635. Available from https://doi.org/10.1016/j.cbpa.2011.08.009.

Huzayyin, A. A., Andreazza, A. C., Turecki, G., Cruceanu, C., Rouleau, G. A., Alda, M., & Young, L. T. (2014). Decreased global methylation in patients with BD who respond to lithium. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *17*, 561–569. Available from https://doi.org/10.1017/S1461145713001569.

Irie, M., Asami, S., Ikeda, M., & Kasai, H. (2003). Depressive state relates to female oxidative DNA damage via neutrophil activation. *Biochemical and Biophysical Research Communications*, *311*, 1014–1018.

Irie, M., Asami, S., Nagata, S., Miyata, M., & Kasai, H. (2002). Psychological mediation of a type of oxidative DNA damage, 8-hydroxydeoxyguanosine, in peripheral blood leukocytes of non-smoking and non-drinking workers. *Psychotherapy and Psychosomatics*, *71*, 90–96. Available from https://doi.org/10.1159/000049351.

Irie, M., Tamae, K., Iwamoto-Tanaka, N., & Kasai, H. (2005). Occupational and lifestyle factors and urinary 8-hydroxydeoxyguanosine. *Cancer Science*, *96*, 600–606. Available from https://doi.org/10.1111/j.1349-7006.2005.00083.x.

Jacoby, A. S., Vinberg, M., Poulsen, H. E., Kessing, L. V., & Munkholm, K. (2016). Increased DNA and RNA damage by oxidation in patients with bipolar I disorder. *Translational Psychiatry*, *6*, e867. Available from https://doi.org/10.1038/tp.2016.141.

Jeong, H., Dimick, M. K., Sultan, A., Duong, A., Park, S. S., El Soufi El Sabbagh, D., … Andreazza, A. C. (2020). Peripheral biomarkers of mitochondrial dysfunction in adolescents with BD. *Journal of Psychiatric Research*, *123*, 187–193. Available from https://doi.org/10.1016/j.jpsychires.2020.02.009.

Jewett, B. E., Miller, M. N., Ligon, L. A., Carter, Z., Mohammad, I., & Ordway, G. A. (2020). Rapid and temporary improvement of depression and anxiety observed following niraparib administration: A case report. *BMC Psychiatry*, *20*, 171. Available from https://doi.org/10.1186/s12888-020-02590-4.

Jimenez-Fernandez, S., Gurpegui, M., Diaz-Atienza, F., Perez-Costillas, L., Gerstenberg, M., & Correll, C. U. (2015). Oxidative stress and antioxidant parameters in patients with major depressive disorder compared to healthy controls before and after antidepressant treatment: Results from a *meta*-analysis. *The Journal of Clinical Psychiatry*, *76*, 1658–1667. Available from https://doi.org/10.4088/JCP.14r09179.

Kakiuchi, C., Ishiwata, M., Kametani, M., Nelson, C., Iwamoto, K., & Kato, T. (2005). Quantitative analysis of mitochondrial DNA deletions in the brains of patients with BD and schizophrenia. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *8*, 515–522. Available from https://doi.org/10.1017/S1461145705005213.

Kato, T. (2017). Neurobiological basis of BD: Mitochondrial dysfunction hypothesis and beyond. *Schizophrenia Research*, *187*, 62–66. Available from https://doi.org/10.1016/j.schres.2016.10.037.

Kato, T. (2019). Current understanding of BD: Toward integration of biological basis and treatment strategies. *Psychiatry and Clinical Neurosciences*, *73*, 526–540. Available from https://doi.org/10.1111/pcn.12852.

Kato, T., Stine, O. C., McMahon, F. J., & Crowe, R. R. (1997). Increased levels of a mitochondrial DNA deletion in the brain of patients with BD. *Biological Psychiatry*, *42*, 871–875. Available from https://doi.org/10.1016/S0006-3223(97)00012-7.

Kawanishi, S., Hiraku, Y., & Oikawa, S. (2001). Mechanism of guanine-specific DNA damage by oxidative stress and its role in carcinogenesis and aging. *Mutation Research - Reviews in Mutation Research*, *488*, 65–76. Available from https://doi.org/10.1016/S1383-5742(00)00059-4.

Knorr, U., Simonsen, A. H., Roos, P., Weimann, A., Henriksen, T., Christensen, E.-M., … Kessing, L. V. (2019). Cerebrospinal fluid oxidative stress metabolites in patients with BD and healthy controls: A longitudinal case-control study. *Translational Psychiatry*, *9*, 325. Available from https://doi.org/10.1038/s41398-019-0664-6.

Kowaltowski, A. J. (2000). Alternative mitochondrial functions in cell physiopathology: Beyond ATP production. *Brazilian Journal of Medical and Biological Research*, *33*, 241–250. Available from https://doi.org/10.1590/S0100-879X2000000200014.

Larsen, N. B., Rasmussen, M., & Rasmussen, L. J. (2005). Nuclear and mitochondrial DNA repair: Similar pathways? *Mitochondrion*, *5*, 89–108. Available from https://doi.org/10.1016/j.mito.2005.02.002.

Lindqvist, D., Dhabhar, F. S., James, S. J., Hough, C. M., Jain, F. A., Bersani, F. S., … Mellon, S. H. (2017). Oxidative stress, inflammation and treatment response in major depression. *Psychoneuroendocrinology*, *76*, 197–205. Available from https://doi.org/10.1016/j.psyneuen.2016.11.031.

Machado-Vieira, R. (2018). Lithium, stress, and resilience in BD: Deciphering this key homeostatic synaptic plasticity regulator. *Journal of Affective Disorders*, *233*, 92–99. Available from https://doi.org/10.1016/j.jad.2017.12.026.

Maes, M., Landucci Bonifacio, K., Morelli, N. R., Vargas, H. O., Barbosa, D. S., Carvalho, A. F., & Nunes, S. O. V. (2019). Major differences in neurooxidative and neuronitrosative stress pathways between major depressive disorder and types I and II BD. *Molecular Neurobiology*, *56*, 141–156. Available from https://doi.org/10.1007/s12035-018-1051-7.

Maes, M., Mihaylova, I., Kubera, M., Uytterhoeven, M., Vrydags, N., & Bosmans, E. (2009). Increased 8-hydroxy-deoxyguanosine, a marker of oxidative damage to DNA, in major depression and myalgic encephalomyelitis / chronic fatigue syndrome. *Neuro Endocrinology Letters*, *30*, 715–722.

Maletic, V., & Raison, C. (2014). Integrated neurobiology of BD. *Frontiers in Psychiatry*, *5*, 98. Available from https://doi.org/10.3389/fpsyt.2014.00098.

Mamdani, F., Rollins, B., Morgan, L., Sequeira, P. A., & Vawter, M. P. (2014). The somatic common deletion in mitochondrial DNA is decreased in schizophrenia. *Schizophrenia Research*, *159*, 370–375. Available from https://doi.org/10.1016/j.schres.2014.08.026.

Munkholm, K., Peijs, L., Vinberg, M., & Kessing, L. V. (2015). A composite peripheral blood gene expression measure as a potential diagnostic biomarker in BD. *Translational Psychiatry*, *5*, e614. Available from https://doi.org/10.1038/tp.2015.110.

Munkholm, K., Poulsen, H. E., Kessing, L. V., & Vinberg, M. (2015). Elevated levels of urinary markers of oxidatively generated DNA and RNA damage in BD. *Bipolar Disorders*, *17*, 257–268. Available from https://doi.org/10.1111/bdi.12245.

Muraleedharan, A., Menon, V., Rajkumar, R. P., & Chand, P. (2015). Assessment of DNA damage and repair efficiency in drug naïve schizophrenia using comet assay. *Journal of Psychiatric Research*, *68*, 47–53. Available from https://doi.org/10.1016/j.jpsychires.2015.05.018.

Mustak, M. S., Hegde, M. L., Dinesh, A., Britton, G. B., Berrocal, R., Rao, K., … Rao, T. S. S. (2010). Evidence of altered DNA integrity in the brain regions of suicidal victims of bipolar depression. *Indian Journal of Psychiatry*, *52*, 220–228. Available from https://doi.org/10.4103/0019-5545.70974.

Odemis, S., Tuzun, E., Gulec, H., Semiz, U. B., Dasdemir, S., Kucuk, M., … Küçükali, C. I. (2016). Association between polymorphisms of DNA repair genes and risk of schizophrenia. *Genetic Testing and Molecular Biomarkers*, *20*, 11–17. Available from https://doi.org/10.1089/gtmb.2015.0168.

Ordway, G. A., Szebeni, A., Hernandez, L. J., Crawford, J. D., Szebeni, K., Chandley, M. J., … Brown, R. W. (2017). Antidepressant-like actions of inhibitors of Poly(ADP-Ribose) polymerase in rodent models. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *20*, 994–1004. Available from https://doi.org/10.1093/ijnp/pyx068.

Özerdem, A., & Ceylan, D. (2021). *Neurooxidative and neuronitrosative mechanisms in BD: Evidence and implications*. *Neurobiology of BD* (pp. 71–83). Elsevier. Available from http://doi.org/10.1016/B978-0-12-819182-8.00006-5.

Ozerdem, A., Ho, A. M. C., Ceylan, D., Armasu, S. M., Winham, S. J., Stockmeier, C. A., … Veldic, M. (2019). F89. Differential DNA repair gene promoter methylation in anterior temporopolar area gray matter in BD. *Biological Psychiatry*, *85*, S247. Available from https://doi.org/10.1016/j.biopsych.2019.03.626.

Perron, B. E., Howard, M. O., Nienhuis, J. K., Bauer, M. S., Woodward, A. T., & Kilbourne, A. M. (2009). Prevalence and burden of general medical conditions among adults with bipolar I disorder: Results from the National Epidemiologic Survey on alcohol and related conditions. *The Journal of Clinical Psychiatry*, *70*, 1407–1415. Available from https://doi.org/10.4088/JCP.08m04586yel.

Prakash, A., & Doublié, S. (2015). Base excision repair in the mitochondria. *Journal of Cellular Biochemistry*, *116*, 1490–1499. Available from https://doi.org/10.1002/jcb.25103.

Recart, V. M., Spohr, L., Soares, M. S. P., de Mattos, B., da, S., Bona, N. P., … Spanevello, R. (2021). Gallic acid protects cerebral cortex, hippocampus, and striatum against oxidative damage and cholinergic dysfunction in an experimental model of manic-like behavior: Comparison with lithium effects. *International Journal of Developmental Neuroscience: The Official Journal of the International Society for Developmental Neuroscience*. Available from https://doi.org/10.1002/jdn.10086.

Rosenblat, J. D., & McIntyre, R. S. (2017). BD and immune dysfunction: Epidemiological findings, proposed pathophysiology and clinical implications. *Brain Sciences*, *7*. Available from https://doi.org/10.3390/brainsci7110144.

Rosenblat, J. D., & McIntyre, R. S. (2018). Efficacy and tolerability of minocycline for depression: A systematic review and *meta*-analysis of clinical trials. *Journal of Affective Disorders*, *227*, 219–225. Available from https://doi.org/10.1016/j.jad.2017.10.042.

Saadat, M., Mohammadynejad, P., Ghanizadeh, A., & Saadat, I. (2012). Genetic polymorphisms (at codons 194 and 399) in the DNA repair gene XRCC1 and susceptibility to BD. *Psychiatry Research*, *198*, 171. Available from https://doi.org/10.1016/j.psychres.2012.01.021.

Sabunciyan, S., Kirches, E., Krause, G., Bogerts, B., Mawrin, C., Llenos, I. C., & Weis, S. (2007). Quantification of total mitochondrial DNA and mitochondrial common deletion in the frontal cortex of patients with schizophrenia and BD. *Journal of Neural Transmission (Vienna, Austria: 1996)*, *114*, 665–674. Available from https://doi.org/10.1007/s00702-006-0581-8.

Sequeira, A., Martin, M. V., Rollins, B., Moon, E. A., Bunney, W. E., Macciardi, F., … Vawter, M. P. (2012). Mitochondrial mutations and polymorphisms in psychiatric disorders. *Frontiers in Genetics.*, *3*. Available from https://doi.org/10.3389/fgene.2012.00103.

Shao, L., Martin, M. V., Watson, S. J., Schatzberg, A., Akil, H., Myers, R. M., … Vawter, M. P. (2008). Mitochondrial involvement in psychiatric disorders. *Annals of Medicine*, *40*, 281–295. Available from https://doi.org/10.1080/07853890801923753.

Shao, L., Young, L. T., & Wang, J.-F. (2005). Chronic treatment with mood stabilizers lithium and valproate prevents excitotoxicity by inhibiting oxidative stress in rat cerebral cortical cells. *Biological Psychiatry*, *58*, 879–884. Available from https://doi.org/10.1016/J.BIOPSYCH.2005.04.052.

Shaughnessy, D. T., McAllister, K., Worth, L., Haugen, A. C., Meyer, J. N., Domann, F. E., … Tyson, F. L. (2015). Mitochondria, energetics, epigenetics, and cellular responses to stress.

Environmental Health Perspectives, *122*, 1271–1278. Available from https://doi.org/10.1289/ehp.1408418.

Sliwinska, A., Sitarek, P., Toma, M., Czarny, P., Synowiec, E., Krupa, R., ... Sliwinski, T. (2017). Decreased expression level of BER genes in Alzheimer's disease patients is not derivative of their DNA methylation status. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *79*, 311–316. Available from https://doi.org/10.1016/j.pnpbp.2017.07.010.

Soeiro-de-Souza, M. G., Andreazza, A. C., Carvalho, A. F., Machado-Vieira, R., Young, L. T., & Moreno, R. A. (2013). Number of manic episodes is associated with elevated DNA oxidation in bipolar I disorder. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *16*, 1505–1512. Available from https://doi.org/10.1017/S1461145713000047.

Sriram, C. S., Jangra, A., Gurjar, S. S., Hussain, M. I., Borah, P., Lahkar, M., ... Bezbaruah, B. K. (2015). Poly (ADP-ribose) polymerase-1 inhibitor, 3-aminobenzamide pretreatment ameliorates lipopolysaccharide-induced neurobehavioral and neurochemical anomalies in mice. *Pharmacology, Biochemistry, and Behavior*, *133*, 83–91. Available from https://doi.org/10.1016/j.pbb.2015.03.022.

Stehling, O., & Lill, R. (2013). The role of mitochondria in cellular iron-sulfur protein biogenesis: Mechanisms, connected processes, and diseases. *Cold Spring Harbor. Perspectives in Biology*, *5*. Available from https://doi.org/10.1101/cshperspect.a011312.

Szebeni, A., Szebeni, K., DiPeri, T. P., Johnson, L. A., Stockmeier, C. A., Crawford, J. D., ... Ordway, G. A. (2016). Elevated DNA oxidation and DNA repair enzyme expression in brain white matter in major depressive disorder. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *20*, pyw114. Available from https://doi.org/10.1093/ijnp/pyw114.

Takao, M., Aburatani, H., Kobayashi, K., & Yasui, A. (1998). Mitochondrial targeting of human DNA glycosylases for repair of oxidative DNA damage. *Nucleic Acids Research*, *26*, 2917–2922. Available from https://doi.org/10.1093/nar/26.12.2917.

Tervasmäki, A., Mantere, T., Hartikainen, J. M., Kauppila, S., Lee, H.-M., Koivuluoma, S., ... Pylkäs, K. (2018). Rare missense mutations in *RECQL* and *POLG* associate with inherited predisposition to breast cancer. *International Journal of Cancer. Journal International du Cancer*, *142*, 2286–2292. Available from https://doi.org/10.1002/ijc.31259.

Topak, O. Z., Ozdel, O., Dodurga, Y., & Secme, M. (2018). An evaluation of the differences in DNA damage in lymphocytes and repair efficiencies in patients with schizophrenia and schizoaffective disorder. *Schizophrenia Research*. Available from https://doi.org/10.1016/j.schres.2018.06.052.

Torrell, H., Montaña, E., Abasolo, N., Roig, B., Gaviria, A. M., Vilella, E., & Martorell, L. (2013). Mitochondrial DNA (mtDNA) in brain samples from patients with major psychiatric disorders: Gene expression profiles, MtDNA content and presence of the MtDNA common deletion. *American Journal of Medical Genetics Part B Neuropsychiatric Genetics*, *162*, 213–223. Available from https://doi.org/10.1002/ajmg.b.32134.

Tsai, M.-C., & Huang, T.-L. (2015). Thiobarbituric acid reactive substances (TBARS) is a state biomarker of oxidative stress in bipolar patients in a manic phase. *Journal of Affective Disorders*, *173*, 22–26. Available from https://doi.org/10.1016/j.jad.2014.10.045.

Tubbs, A., & Nussenzweig, A. (2017). Endogenous DNA damage as a source of genomic instability in cancer. *Cell*, *168*, 644–656. Available from https://doi.org/10.1016/j.cell.2017.01.002.

Valentina, P., Ekaterina, Y., Nikolay, B., & Evgenii, P. (2020). The effect of organic lithium salts on plasma 8-hydroxy-2'-deoxyguanosine in bipolar patients in vitro. *Psychopharmacology Bulletin*, *50*, 19–27. Available from https://pubmed.ncbi.nlm.nih.gov/32214518/.

Valvassori, S. S., Resende, W. R., Dal-Pont, G., Sangaletti-Pereira, H., Gava, F. F., Peterle, B. R., … Quevedo, J. (2017). Lithium ameliorates sleep deprivation-induced mania-like behavior, hypothalamic-pituitary-adrenal (HPA) axis alterations, oxidative stress and elevations of cytokine concentrations in the brain and serum of mice. *Bipolar Disorders*, *19*, 246–258. Available from https://doi.org/10.1111/bdi.12503.

Vancampfort, D., Vansteelandt, K., Correll, C. U., Mitchell, A. J., De Herdt, A., Sienaert, P., … De Hert, M. (2013). Metabolic syndrome and metabolic abnormalities in BD: A *meta*-analysis of prevalence rates and moderators. *American Journal of Psychiatry*, *170*, 265–274. Available from https://doi.org/10.1176/appi.ajp.2012.12050620.

Wang, C. C., Chen, W. L., Lin, C. M., Lai, C. H., Loh, C. H., Chen, H. I., & Liou, S. H. (2016). The relationship between plasma and urinary 8-hydroxy-2-deoxyguanosine biomarkers measured by liquid chromatography tandem mass spectrometry. *Environmental Science and Pollution Research.*, *23*, 17496–17502. Available from https://doi.org/10.1007/s11356-016-6898-4.

Wang, J., Feng, H., Zhang, J., & Jiang, H. (2013). Lithium and valproate acid protect NSC34 cells from H2O2-induced oxidative stress and upregulate expressions of SIRT3 and CARM1. *Neuro Endocrinology Letters*, *34*, 648–654.

Watts, M. E., Pocock, R., & Claudianos, C. (2018). Brain energy and oxygen metabolism: Emerging role in normal function and disease. *Frontiers in Molecular Neuroscience*, *11*, 216. Available from https://doi.org/10.3389/fnmol.2018.00216.

Wei, Y. C., Zhou, F. L., He, D. L., Bai, J. R., Hui, L. Y., Wang, X. Y., & Nan, K. J. (2009a). The level of oxidative stress and the expression of genes involved in DNA-damage signaling pathways in depressive patients with colorectal carcinoma. *Journal of Psychosomatic Research*, *66*, 259–266. Available from https://doi.org/10.1016/j.jpsychores.2008.09.001.

Wei, Y.-C., Zhou, F.-L., He, D.-L., Bai, J.-R., Ding, H., Wang, X.-Y., & Nan, K.-J. (2009b). Oxidative stress in depressive patients with gastric adenocarcinoma. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *12*, 1089–1096. Available from https://doi.org/10.1017/S1461145709000091.

Yakes, F. M., & Van Houten, B. (1997). Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in human cells following oxidative stress. *Proceedings of the National Academy of Sciences (USA).*, *94*, 514–519. Available from https://doi.org/10.1073/pnas.94.2.514.

Yang, Y., Wu, N., Tian, S., Li, F., Hu, H., Chen, P., … Zhuang, J. (2016). Lithium promotes DNA stability and survival of ischemic retinal neurocytes by upregulating DNA ligase IV. *Cell Death and Disease*, *7*. Available from https://doi.org/10.1038/cddis.2016.341.

Zanni, G., di Martino, E., Omelyanenko, A., Andäng, M., Delle, U., Elmroth, K., & Blomgren, K. (2015). Lithium increases proliferation of hippocampal neural stem/progenitor cells and rescues irradiation-induced cell cycle arrest in vitro. *Oncotarget*, *6*, 37083–37097. Available from https://doi.org/10.18632/oncotarget.5191.

Zanni, G., Goto, S., Fragopoulou, A. F., Gaudenzi, G., Naidoo, V., Di Martino, E., … Blomgren, K. (2021). Lithium treatment reverses irradiation-induced changes in rodent neural progenitors and rescues cognition. *Molecular Psychiatry*, *26*, 322–340. Available from https://doi.org/10.1038/s41380-019-0584-0.

Zhang, Q., Zhang, Q., Li, H., Zhao, X., & Zhang, H. (2021). LiCl induces apoptosis via CHOP/NOXA/Mcl-1 axis in human choroidal melanoma cells. *Cancer Cell International*, *21*, 96. Available from https://doi.org/10.1186/s12935-021-01778-2.

Zhou, F., Zhang, W., Wei, Y., Zhou, D., Su, Z., Meng, X., ... Tian, W. (2007). The changes of oxidative stress and human 8-hydroxyguanine glycosylase1 gene expression in depressive patients with acute leukemia. *Leukemia Research*, *31*, 387–393. Available from https://doi.org/10.1016/j.leukres.2006.07.014.