Chapter 10

Mechanisms of aging in bipolar disorder

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10.1 Introduction

Population aging is a worldwide phenomenon. Due to improvements in general socio-economic conditions, better access to health care, better treatments, we are observing a growing number of individuals with bipolar disorder (BD) reaching the "golden age." Nonetheless, this population presents with an accelerated aging phenotype, manifested by higher rates of age-related medical problems, cognitive impairment, higher risk for dementia, higher mortality rates compared to nonpsychiatric populations. Yet, there is a paucity of data on the putative mechanisms linking BD to this accelerated aging clinical phenotype.

Recently, there has been a growing interest in the search for the hallmarks or pillars of biological aging. Biological aging is a complex but still poorly understood process. It probably involves the concerted, interconnected changes in multiple biological pathways that ultimately lead to the accumulation of damage in cells and tissues. Detailed reviews about the processes that drive biological aging and the current challenges of measuring biological aging have been previously published (López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013). The most commonly accepted hallmarks of biological aging are cellular senescence, telomere attrition, mitochondria dysfunction, genomic instability, epigenetic alterations, stem cell exhaustion, loss of proteostasis, altered intercellular communication, and deregulated nutrient sensing.

10.2 Cellular senescence and telomere attrition in bipolar disorder

Telomere attrition is one of the most robust markers of replicative cellular senescence. The telomeres are specialized structures of nucleoprotein

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complexes, consisting of a variable number of tandem repeats of double-stranded TTAGGG nucleotide sequence and a 3′-rich single-stranded overhang that function as a "cap" at the chromosome end (Lu, Zhang, Liu, Songyang, & Wan, 2013). Due to the inability of the DNA polymerase complex to replicate the 3′-end of the lagging strand linear chromosomes, telomere length (TL) gradually decreases with every cell division (Blackburn, Epel, & Lin, 2015). When the TL reaches a critical length, cell functioning becomes unstable, leading to cellular senescence.

Many studies evaluated the association between TL and BD. Early reports showed mostly nonsignificant differences between BD patients and nonpsychiatric controls (Colpo et al., 2015). However, earlier studies have shown a different trend, with BD patients having shorter TL compared to controls (Huang, Wang, Tseng, Hung, & Lin, 2018). Some studies also addressed the association of TL with specific characteristics of BD. For example, Lima et al. (2015) did not find a significant difference in TL between BD1 and BD2 patients. Individuals with late-stage BD had significantly reduced TL compared to those with early-stage BD (Huang et al., 2018). Interestingly, some studies showed that psychiatrically well siblings of relatives BD patients had shorter TL compared to unrelated psychiatrically well controls (Vasconcelos-Moreno et al., 2017) (PMID: 28339618), suggesting that telomere attrition and cellular senescence are possible trait characteristics and an endophenotype of BD.

It is important to note several caveats in the association between BD and TL. Most studies usually included small sample sizes and *meta*-analyses showed evidence of high heterogeneity across studies what may significantly bias the results. The TL analyses were done mostly in peripheral cells (e.g., leukocytes) and studies with postmortem brain tissues did not show a significant difference between BD and control groups (Fries et al., 2020; Zhang, Cheng, Craig, Redman, & Liu, 2010). Thus to what extend peripheral TL reflects brain cells TL is not clear, and the differences between peripheral and brain TL may indicate different dynamics in the control of cellular senescence in BD.

10.3 Epigenetic alterations, DNA damage, and genomic instability

Epigenetics changes, including DNA methylation and the expression of noncoding RNA (e.g., microRNAs), are considered important hallmarks of biological aging. Over the past decade, several studies showed the association between whole-genome DNA methylation and chronological age and its links to adverse health outcomes, like increased mortality risk (Horvath et al., 2012; Petkovich et al., 2017). These early evidences showing the DNA methylation were tightly correlated with chronological age, and the availability of large datasets led to the development of statistical algorithms aiming

to predict someone's biological aging. The epigenetics clock could then reliably predict the individual biological age and identify those who had higher biological age (predicted age, based on DNA methylation, higher than chronological age) or lower biological age (predicted age, based on DNA methylation, lower than chronological age) (Horvath, 2013). An important feature of the epigenetic clock is that it can be measured in specific tissues and allowing the calculation of tissue-specific biological aging.

Few studies investigated if subjects with BD was associated with higher biological age, based on DNA methylation patterns. In a series of analysis including postmortem brain tissue and peripheral immune blood cells, there was evidence for accelerated biological aging only among older adults with BD, possibly suggesting a significant age-by-disease effect on epigenetic clocks (Fries et al., 2017, 2020).

Genomic instability is another major hallmark of biological aging. DNA damage can manifest in different forms, including the double-strand and single-strand breaks, small base chemical alteration, helix distorting lesions, and DNA oxidation (Ross & Truant, 2017). DNA damage triggers the DNA damage response (DDR) in the cell which includes a myriad of cellular events aimed to repair the DNA. The DDR is usually capable to repair the damaged DNA, but when it is overwhelmed and cannot fully repair the damage DNA, it results in genomic instability, with two major consequences: cellular senescence and programmed cell death; or unchecked cellular replication.

Several studies investigated the association between markers of DNA damage [e.g., 8-deoxyguanosine (8-OHdG)] in blood and urine. These studies have consistently shown that markers of DNA damage are elevated in individuals with BD (Andreazza et al., 2007; Jacoby, Vinberg, Poulsen, Kessing, & Munkholm, 2016; Munkholm, Poulsen, Kessing, & Vinberg, 2015). The increased levels of DNA damage markers are present even during euthymic state (Ceylan et al., 2018) and accompanied by decreased efficiency in the DNA base excision repair system (Ceylan et al., 2018). Moreover, a recent study evaluating DNA markers in BD patients and unaffected first-degree relatives (UR) also demonstrated that both groups had higher levels of DNA damage markers, but no differences among BD and UR groups, indicating that DNA damage can also be an endophenotypic marker of this disorder (Coello et al., 2021).

10.4 Mitochondria dysfunction

There is a wealth of evidence linking BD to mitochondrial dysfunction. Several original studies and *meta*-analyses have demonstrated that BD patients have higher levels of oxidative stress markers, one of the main indicators of mitochondrial dysfunction (Jiménez-Fernández et al., 2021). Beyond the measurement of oxidative stress markers in body fluids, other

studies also confirmed a significant impairment in mitochondrial function in BP. For example, magnetic resonance spectroscopy studies demonstrated higher lactate levels in the brain of BD patients compared to healthy controls (Kuang, Duong, Jeong, Zachos, & Andreazza, 2018; Soeiro-de-Souza et al., 2016). Postmortem and in vivo studies have also demonstrated a significant decrease in the activity of the complex I unit of the mitochondrial respiratory chain, which significantly correlates with increased production of oxidative stress markers (Akarsu et al., 2015; Andreazza, Shao, Wang, & Young, 2010; de Sousa et al., 2015).

More recently, studies have focused on changes in the mitochondrial DNA (mtDNA) copy number as a marker of mitochondrial function in BD. Early studies did not support an association between decreased mtDNA copy number, an indirect marker of mitochondrial dysfunction, in patients with BD (de Sousa et al., 2014). More recently, there has been evidence of decreased mtDNA copy number in BD, especially in those with BD type 1 (Chung, Ahn, Kim, & Joo, 2020) and during manic and depressive phases of the disorder (Wang et al., 2018). Also, there is emerging evidence that the abnormalities in the mtDNA copy may be moderated by race, with Asians being significantly more affected than patients from other racial groups (Yamaki et al., 2018).

10.5 Altered intercellular communication

The concept of intercellular communication is broad and can virtually encompass almost any known physiological function. It is usually defined as "the transfer of information from one cell to another, either by direct contact with each other or by the release of a substance from one cell that is taken up by another cell" (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/intercellular-communication). Hormones are a classic form of intercellular communication since they are secreted by specific cell types (e.g., the thyroid-stimulating hormone by the pituitary) and influence the activity and function of a cell at distant sites (e.g., the production and release of T3 and T4 hormones by follicular cells in the thyroid glands). Nonetheless, a myriad of other circulating biomarkers can also convey biological information from one cell to another in a paracrine or endocrine fashion, such as inflammatory cytokines, trophic factors, and tissue remodeling molecules.

One strong candidate marker of altered intercellular communication is the "Inflammaging" concept, which posits that there is a gradual shift of the immune-inflammatory response in older adults toward a mild, chronic pro-inflammatory profile, even in the absence of pathogens ("sterile inflammation") (Franceschi et al., 2007). A major consequence of the Inflammaging process is the systemic decline in function and predisposition to age-related diseases (Ferrucci & Fabbri, 2018).

There is abundant evidence in the literature showing the association of BD with abnormalities in the immune-inflammatory response, mostly the unchecked elevation of pro-inflammatory cytokines. Previous *meta*-analyses have shown that inflammatory markers like the IL-6 and TNF-α and its soluble receptor 1 (sTNFr1) are significantly elevated in the BD, independent of the disease phase (Modabbernia, Taslimi, Brietzke, & Ashrafi, 2013; Rowland et al., 2018). Beyond their role in controlling the inflammatory response, these cytokines are regarded as effectors of the Inflammaging process and triggers of cellular senescence processes (Chinta et al., 2015; Schafer et al., 2020).

It is noteworthy that the elevation of these pro-inflammatory cytokines is present in BD patients with clinical manifestations commonly associated with aging, like cognitive dysfunction and medical comorbidity. For example, IL6 plasma levels were negatively associated with global cognitive performance (Barbosa et al., 2018), while TNF-α levels were associated with worse inhibitory control, a key executive function component, in remitted BD 1 patients, even at early disease stages (Barbosa et al., 2012; Chakrabarty, Torres, Bond, & Yatham, 2019; Hua et al., 2021).

There is a growing interest in staging BD into early versus late-stage disease in recent years, which may bear important clinical, prognostic, and biological implications. Those classified with late-stage BD tend to have chronic disease course, with more medical comorbidities and worse cognitive performance (Kapczinski et al., 2014). When studies evaluated the pro-inflammatory cytokine levels in BD patients divided according to the disease stage, they mostly found an elevation of pro-inflammatory cytokines (e.g., TNF-α and IL-6) among those with late-stage disease (Castaño-Ramírez et al., 2018; Grande et al., 2014). Interestingly, the levels of eotaxin/CCL-11, a chemokine that has been considered a driver of brain aging (Villeda et al., 2011), is elevated in those with late-stage BD, providing further evidence that late-stage BD is a harbinger of accelerated aging among patients with BD (Panizzutti et al., 2015).

10.6 Concluding remarks

The recent availability of large neuroimaging databases (e.g., the ENIGMA group) and advances in mathematical modeling and machine learning procedures has allowed the inquiry if BD patients have an accelerated brain age compared to healthy individuals. Findings of accelerated brain age in BD (i.e., predicted brain age greater than chronological age) would be major evidence that BD is accompanied by age-related biological changes that ultimately reflected in brain structural and functional changes.

However, the studies published so far have produced conflicting evidence of accelerated brain age in BD. Studies have shown that BD patients have greater predicted age than chronological age based on cortical measures

TABLE 10.1 Strength of association between changes in the hallmarks of biological aging and bipolar disorder.

Hallmark of biological aging in bipolar disorder	Evidence
Altered intercellular communication (e.g., Inflammaging)	[a]
Mitochondrial dysfunction and deregulation of nutrient sensing	[a]
Epigenetic clock alterations	[b]
Telomere attrition	[b]
Genomic instability	[b]
Loss of proteostasis	[c]
Stem cell exhaustion	[c]
Predicted brain age versus chronological age (structural MRI)	[b]

[a] *Strong evidence.*
[b] *Conflicting evidence.*
[c] *No evidence available in the literature.*

structural MRI data (Shahab et al., 2019; Van Gestel et al., 2019) and white matter diffusion tension imaging data (Rokicki et al., 2021). Other studies using cortical measures MRI data failed to show an accelerated age profile among BD patients (Hajek et al., 2019; Nenadić, Dietzek, Langbein, Sauer, & Gaser, 2017; Tønnesen et al., 2020). These conflicting results highlight the highly heterogeneous nature of BD, along with several methodological differences across studies, making it more difficult to compare their results (Table 10.1).

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