An inflamed mood
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Chapter 1

General Introduction
Major depressive disorder

Major depressive disorder (MDD) is the second leading cause of disability globally because of its high prevalence, and its impact in terms of functioning, physical health and longevity [1]. In clinical practice, the unclear etiology and diverse presentations of MDD generate substantial obstacles for an accurate diagnosis and effective treatment [2]. Clearly, both aspects will benefit from the elucidation of pathophysiological processes involved and the identification of biological markers for MDD. Given the many pathophysiological processes involved in MDD, such as dysfunctions of neurotransmitter systems, neurotrophic factors and the inflammatory system [3] it is understandable that studies based on descriptive diagnostic classifications yielded mixed results and were difficult to replicate [2]. This has seriously hindered research into the underlying mechanisms of depression [4]. It is thus necessary to develop a better diagnostic classification system, for instance based on biological markers as well as clinical presentation, in order to improve the homogeneity of patient groups with the same diagnosis [5].

Subtypes of MDD

MDD is a highly heterogeneous syndrome with a wide range of symptoms. According to the DSM-IV classification, MDD can have 227 symptom combinations [6]. Furthermore, the newly published DSM-5 still defines MDD as a clinical syndrome rather than a disease, in which the diagnostic criteria of MDD are based on descriptive classification and phenomenological principles, with the core symptoms of depressed mood and/or lack of interest or pleasure [7].

Historically, subtyping of MDD has been based on symptom presentation, severity, onset characteristics and course of illness, with the aim to advance both clinical management and scientific research. Well-established clinical subtypes are based on cross-sectional symptom features and include melancholic, psychotic, atypical and anxious depression. Other subtyping approaches have also been proposed, based on the onset of illness, course of disease, and severity etc. [8]. However, subtyping is still far from perfect given the considerable overlap of MDD characteristics.

A well-designed subtyping strategy should meet the following criteria: first, the subtype aids the choice of treatment strategy; second, the subtype helps to predict treatment response and prognosis; or third, the subtype depicts specific genetic and/or neurobiological characteristics [8]. Several studies have shown that MDD subtypes display different inflammatory marker profiles [9, 10]. Moreover, treatment resistance may be associated with levels of inflammatory markers [11, 12]. Accordingly subtyping of MDD on the basis of inflammatory markers could be a promising strategy.

Links between inflammation and depression

The pathophysiology of MDD is far from clear. In this respect several hypotheses have been proposed, such as the monoamine hypothesis, neurogenesis/neuroplasticity hypothesis, stress hypothesis, immune-inflammation hypothesis and glutamate hypothesis. It is important to note that these proposed pathophysiological mechanisms do not act separately but coexist and
interact with each other in a complex manner, which may partly explain the divergent symptom profiles in MDD.

An involvement of the inflammatory system in depression has already been reported decades ago [13, 14], since then accumulating evidence has been presented for its involvement in the etiology and pathophysiology of MDD. At an early stage the interest in inflammatory processes was limited to the fields of immunology and infectious diseases. The brain was considered to be an immune privileged organ which was largely unaffected by peripheral immune changes because of the existence of the blood-brain barrier (BBB). As a result, the effects of peripheral immune changes on brain function status were generally ignored except for those sporadic cases when the BBB was seriously damaged. More recently it was recognized that MDD is associated with a hyperactive inflammatory response system but also with peripherally elevated concentrations of pro-inflammatory mediators such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, and C-reactive protein (CRP) [15-17]. Furthermore, some studies also demonstrated that the levels of certain peripheral inflammatory markers were associated with the outcome of antidepressant treatment [18, 19]. Supportive evidence also came from studies of single nucleotide polymorphisms (SNPs), showing a role of gene variants in the etiology of depression [20, 21]. For example, people carrying the functional genetic variant rs1800795, a SNP in the IL-6 promoter region, tended to have higher blood levels of IL-6, but also a higher incidence of depression than non-carriers [22]. Genomic studies can aid in the identification of biological pathways involved in the pathophysiology of MDD, but as yet results have been mixed even in genome-wide association studies (GWAS) with a huge sample size [21, 23].

Cytokines play an essential role in brain development, and also serve to maintain healthy brain function by sustaining neuronal survival, neurogenesis, and synaptic plasticity [24]. Thus, dysregulation of cytokines would interfere brain functioning and even its structure. For instance, peripheral inflammatory markers were found to be significantly increased in patients with MDD and capable of entering the brain and to interact with well-known pathophysiological processes involved in depression, including neurotransmitter synthesis and metabolism, neuroendocrine function, and neuroplasticity. In fact, hyperactivity of inflammatory pathways within the brain is considered to reduce neurotrophic factors, to disrupt the glutamate release/re-uptake balance, and to enhance oxidative stress, leading to excitatory neurotoxicity followed by neuronal and glial cell damage, which is consistent with the neuropathology of MDD [25, 26]. In addition, psychosocial stress can also interact with the inflammatory system through activation of the hypothalamic-pituitary-adrenal (HPA)-axis and sympathetic system [27, 28] (see Figure.1 Bio-connections between the stress, inflammatory cytokines and brain). Conversely depression can facilitate the inflammatory response by the interaction between the HPA axis and cytokines, in which dysregulated HPA axis functioning, a key characteristic of depression, decreases the inhibitory feedback on the production of cytokines [29, 30]. In this respect, it is also important to note that in children experiencing multiple depressive episodes significantly increased CRP levels were measured during the depressive state [31].
In the end, it is noteworthy that depression is only inflammatory driven in a subgroup of patients, depending on the individual physiological condition including sympathetic/parasympathetic system, HPA axis activity, hippocampal volume, and personality [32].

**Treatment resistant depression**

More than 30% of the depressive patients do not respond satisfactorily to subsequent regular antidepressant treatments, and can be classified as having treatment resistant depression (TRD). TRD is responsible for the largest clinical, personal, and economic burden within MDD [33, 34]. Considerable attention has been paid to treatment strategies and the etiology and underlying pathophysiology of TRD, but progress is slow and as yet far from satisfactory. One of the reasons may be a lack of general consensus on the definition of TRD, although most investigators would define TRD by an insufficient response to at least two different antidepressant treatments. As a result, sample composition and outcomes may vary according to the definitions used.

Both categorical and dimensional approaches have been used to characterize TRD, but both have their shortcomings. The categorical approach emphasizes the number of unsuccessful antidepressant treatments but ignores other forms of treatment such as psychotherapy and physical treatments such as modified electroconvulsive treatment (MECT) and important factors such as family history, personality characteristics and comorbid anxiety [35]. Most dimensional approaches include these variables and stage TRD by rating scores, although they can vary considerably from each other, such as the Massachusetts General Hospital Staging Model (MGH-s), Antidepressant Treatment History Form (ATHF), European staging model (ESM), Thase and Rush staging model (TRSM), and Maudsley Staging Model (MSM) [35]. The dimensional approach is sometimes applied in scientific research but not in clinical practice because of its lack of operability. Furthermore, both
approaches only judge the effective response at the endpoint and do not take into account how long the “effective response” could last, which is an important factor with treatment outcome as well as prognosis. A more comprehensive and exclusive definition of TRD is required for both clinical practice and scientific research.

**Exploration of new strategies for MDD/TRD treatment**

The development of antidepressant medication started in the 1950s with the discovery that tricyclics such as imipramine and monoamine oxidase inhibitors, such as isoniazid, had beneficial effects in the treatment of depression [36, 37]. Thereafter, considerable efforts have been made to develop new antidepressant drugs and strategies, mainly focusing on serotonin and norepinephrine as a key neurotransmitters involved in mood disorders. Nowadays, the common treatments for MDD include psychotherapy, physical treatments, and pharmaceutical treatments, in the form of monotherapy or combined treatment. However, more than 30% of depressed patients develop TRD even after stepwise guideline-based treatments [33, 34]. Given the heavy burden caused by TRD for the individual and society, developing effective treatment strategies is strongly needed. There is growing interest in drugs targeting the inflammatory system, as well as drugs that influence glutamate systems, opioid systems, dopamine systems, and cholinergic systems, which all interact with the inflammatory system and its response [38-41].

**Glutamate system**

The relation of the glutamate system with cognitive function has prompted investigators to investigate the glutamate receptor antagonist ketamine in this respect. Although it is not fully understood how the ketamine exerts its robust and rapid-onset antidepressant effects, substantial studies reported that the subject’s depressive symptoms were significantly improved after 2 hours of ketamine administration and lasted for 1 week [42, 43]. In one study, TRD patients were divided into four groups receiving placebo or S-ketamine (28, 56, and 84 mg, respectively) for 8 weeks [44]. As turned out, the antidepressant effect of S-ketamine was dose-dependent, and in contrast with current antidepressant its onset of action was rapid. Further observation revealed that S-ketamine administration effectively reduced symptoms of depression also in patients formerly subjected to placebo.

S-ketamine has been marketed in the America for antidepressant treatment [45], despite a risk for hallucinogenic and psychotic effects. The emergence of ketamine as an effective and rapid acting antidepressant drug has boosted researchers’ interest in glutamatergic agents. Other antidepressant compounds targeting the glutamate system are currently under investigation [46-48].

**Opioid system**

The opioid system is involved in analgesia and the general regulation of inflammatory responses [49]. It had been found that modulators of the opioid system which were used in the management of pain induced fluctuations and recurrence of depressive symptoms. As a result, the potential of opioid system modulators in antidepressant treatment has attracted researchers’ interests. Buprenorphine, a μ-opioid receptor agonist and a κ-opioid receptor (KOR) antagonist, was shown to possess antidepressant effects [50, 51]; ALKS-5461, a
mixture of buprenorphine and samidorphan, had been approved the positive effects for TRD treatment [52]; and a phase 3b extension study is now under development (ClinicalTrials.gov, Identifier NCT03610048). CERC-501, a short-acting selective antagonist of the KOR receptor, has been shown to augment antidepressant response with TRD treatment in phase I trials [53, 54], and phase II trials are still ongoing (ClinicalTrials.gov, Identifier NCT 01913535).

**Cholinergic system**
Traditionally, the cholinergic system was recognized to be a regulator of cognition and memory [55]. However, it has also been reported that hyperactivity of cholinergic systems may be involved in the pathological mechanism of depression, while nicotine (N) and muscarinic (M) acetyl-choline receptor modulators are expected to be promising candidates for the treatment of depression [56, 57]. One study illustrated that intravenous infusion of scopolamine rapidly exerted antidepressant effects, similar to S-ketamine, by regulating the m-TOR pathway [58]. In addition, SSRIs when combined with oral scopolamine displayed significantly better antidepressant efficacy than SSRIs alone [59]. In addition, mecamylamine, a nicotinic acetylcholine receptors (nACHRs) antagonist and α4β2 antagonist, was effective in the treatment of TRD [60]. CP-601, 927, a partial agonist of nACHRs may also increase leptin levels and also be effective in the treatment of TRD [61].

**Dopamine system**
Some researchers have proposed dopamine D3 receptor (D3R) as an important therapeutic target for TRD treatment [62-64]. For example, buspirone used in the second phase of the STAR*D study possesses regulating effects on the D3R [65, 66], while Cariprazine, a dopamine D2/D3 receptor partial agonist, is a new antipsychotic drug recently approved by FDA for the treatment of schizophrenia and bipolar mania, which was shown D3R-dependent antidepressant effects [62]. Pramipexole is a D2R/D3R agonist that is effective in treating Parkinson’s comorbid depression [67] as well as in TRD treatment [68].

**Immune system**
Meta-analyses have shown that non-steroid anti-inflammatory drugs (NSAIDs) such as celecoxib significantly improved symptoms of MDD without increasing the risk of adverse reactions [69, 70]. Furthermore, the functional tumor necrosis factor antagonist infliximab has been reported to improve depressive symptoms in TRD patients with high baseline levels of inflammatory biomarkers [18]. In addition, a large cohort study has compared the efficacy of SSRI monotherapy with the combination of an SSRI and an anti-inflammatory drug [71]. It appeared that a low-dose acetylsalicylic acid significantly reduced the risk of experiencing a depressive episode [Hazard rate ratio 0.71; 95% confidence interval (0.50; 1.01)], suggesting that combining an SSRI with an immune-modulator can be beneficial for depressive patients.

Inflammation could activate an anxiety-related loop, reduce reward loop conduction, and thus play a role in the development of depression. As a multi-effect pro-inflammatory cytokine, IL-6 holds the properties of being a pro-inflammatory factor or an anti-inflammatory factor [72, 73]. A number of studies have found that the outcome of antidepressant treatment is related to a change in IL-6 levels [74, 75]. IL-6-targeting drugs may be promising for
depression treatment. In addition, studies on omega-3 fatty acids, statins, and intestinal probiotics, which all connect with the immune system, have also demonstrated positive results [76-81]. Considering the heterogeneity of depression and the notion that depression is only inflammatory driven in a subset of depressive patients, anti-inflammatory augmentation strategies should preferably be based on measurements of inflammatory markers such as CRP and IL-6.

Other drug targets
New compounds targeting the neurotrophic system and new non-pharmacological treatments are also expected to benefit TRD patients in the future. On the other hand, newly qualified methods of screening drugs are demanded for the development of innovative drugs. Some researchers have suggested that animal models of TRD need to be improved. For example, it needs to meet four criteria: increased responsiveness to stress; poor response to chronic antidepressant treatments; effective to new antidepressant treatments, like ketamine; consistent with known clinical observations.

Overview of the thesis
This thesis aims to explore the usefulness of inflammatory markers to gain insight in the underlying pathophysiology of MDD/TRD. A second objective is to investigate the efficacy of anti-inflammatory treatment in MDD and more specifically TRD patients with high inflammatory activity.

Chapter 2 reviews the distribution of inflammatory markers including interleukins, tumor necrosis factor-α, and C-reactive protein, in melancholic and non-melancholic depression, exploring the role of inflammatory markers in these well-known clinical subtypes of MDD.

Chapter 3 reviews the validity of blood inflammatory markers in predicting the outcome of TRD treatment. In addition, this review also pays attention to the relation between the changes in levels of inflammatory markers and the severity of depressive symptoms.

Chapter 4 is a pilot case-control study exploring the associations of FKB5 SNPs and haplotypes with susceptibility and treatment response phenotypes in Han Chinese with MDD.

Chapter 5 investigates the associations of CNRI SNPs and haplotypes with vulnerability and treatment response phenotypes in Han Chinese with MDD. This case-control association study was conducted in the same population with chapter 4.

Chapter 6 describes the protocol of a randomized double blind placebo controlled study with N-acetylcysteine as add-on to regular antidepressant medication in TRD, including the rationale, sample, drugs, primary/secondary outcomes, inclusion/exclusion criteria etc.

Chapter 7 is a general discussion on this thesis, including the summary of main findings, methodological considerations, which talks about the strengths and limitations of all studies, the relationship between inflammatory dysregulation and MDD/TRD, and the anti-
inflammatory treatment in MDD/TRD. Lastly, the clinical implications of our findings, and directions for future research will be discussed.
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