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Review

Molecular biomarkers of depression

Anand Gururajan[a], Gerard Clarke[b,c], Timothy G. Dinan[b,c], John F. Cryan[a,b,*]

[a] Dept. Anatomy & Neuroscience, University College Cork, Cork, Ireland
[b] APC Microbiome Institute, University College Cork, Cork, Ireland
[c] Dept. of Psychiatry and NeuroBehavioural Science, University College Cork, Cork, Ireland

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ABSTRACT

Depression is the leading psychiatric disorder worldwide with a significant economic and emotional strain on society. There is a need for robust biomarkers which will help improve diagnosis and accelerate the drug discovery process. These are objective, peripheral physiological indicators whose presence can be used to predict the probability of onset or presence of depression, stratify according to severity or symptomatology, indicate prognosis and predict or track response to therapeutic interventions. In this review, we will address several issues pertaining to biomarkers in depression which will be grouped under the headings transcriptomic, proteomic, genomic and telomeric biomarkers. We will review some of the main pitfalls and also address ethical, moral and legal issues which relate to biomarker use in the clinic. We anticipate that in conjunction with initiatives such as the NIH Research Domain Criteria (RDoC), biomarkers will have a significant role to play in the psychiatric clinic in the years to come with a view to improving the lives of sufferers worldwide.

Contents

* Corresponding author at: Dept. Anatomy & Neuroscience, University College Cork, Cork, Ireland.
E-mail address: j.cryan@ucc.ie (J.F. Cryan).

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1. Introduction

More than a decade ago depression was controversially described at the World Economic Forum as "the cancer of the 21st century" in terms of increasing prevalence, impact on the patient and society and the associated stigma (Holden, 2000). But current global statistics and projections would indeed appear to support such a statement. Recent 2014 WHO data suggests it is currently the leading cause of global disease burden (Smith, 2014) with global prevalence ranging from 3% to 17%, increasing to between 9.3% and 23% when taking into account chronic physical diseases (*e.g.* diabetes, asthma, arthritis) with depression as a comorbidity (Andrade et al., 2003; Moussavi et al., 2007). In adolescents, prevalence is reported to be between 2.8% and 5.6% with females being more affected than males (Costello et al., 2006). At the other end of the age spectrum, prevalence in the geriatric population is 12.3% but increases to up 37.9% in densely urbanised areas (Copeland et al., 2004). Evidence also shows that prevalence is linked to poor diet (Dash et al., 2015) and lower socioeconomic status (Messias et al., 2011).

As with all other psychiatric disorders, the aetiology of depression is incredibly complex implicating psychosocial, genetic, epigenetic, neuroendocrine and neuroimmunological factors (Bienvenu et al., 2011; Li et al., 2011; Nestler, 2014). This complexity has a direct impact on the accuracy with which we diagnose depression and its subtypes (Lakhan et al., 2010), on our understanding of the pathophysiology (Krishnan and Nestler, 2008) and our ability to design and select effective treatment strategies (Alexander and Preskorn, 2014). Currently available pharmacological interventions are largely designed to increase monoamine-based neurotransmission but as shown by the STAR-D trial, patients that had greater disease burden required increasing pharmacotherapy which did not always translate into remission (Warden et al., 2007). Furthermore, they have significant side effect profiles (Anderson et al., 2012) and a delayed onset of action (Harmer et al., 2009) which affect compliance (Sawada et al., 2009). Of late there is increased emphasis on developing novel non-monoamine based strategies for depression such as those focused on the melatonergic system (Llorca, 2010) and the glutamate system (Monteggia and Zarate, 2015; Zarate and Manji, 2008). Non-pharmacological interventions include psychotherapy (Casacalenda et al., 2002), electroconvulsive therapy (ECT-Review-Group, 2003), transcranial magnetic stimulation (TMS) (Carpenter et al., 2012), vagus nerve stimulation (Sackeim et al., 2001) and deep brain stimulation (Holtzheimer and Mayberg, 2011), all of which have shown to be effective to varying degrees and are used in combination with antidepressants but their precise modes of action are unclear.

Over the last two to three decades, there has been a paradigm shift in our approach towards depression from identifying exact causes to focussing on probabilities that an individual has or will get depression (Singh and Rose, 2009). Biomarkers are essential in advancing this strategy and in this review we highlight the evidence which supports the use of several that have the potential to aid diagnosis, indicate prognosis and predict response to different therapeutic strategies. Perhaps, more importantly, the evidence will advance our understanding of the pathophysiology of depression.

2. Biomarkers

In other areas of medicine, diagnostic probabilities are defined by validated biomarkers which are 'objective physiological indicators of normal biological processes, pathogenic processes or response to a specific therapeutic intervention' (Biomarker-Definitions-Working-Group, 2001). The diagnosis of depression is symptom based due to the lack of biological signatures which adequately fulfil these latter two criteria. Biomarkers fall into three different categories, namely trait, state and endophenotype. Trait biomarkers are permanent and indicate the existence of pathology prior to the onset of the disorder, during and even after remission. They are useful in making predictions about whether an individual will develop a disorder. State biomarkers are temporary, reflect the clinical status of the individual and are present prior to the onset and during the disorder but are normalised in remission. Endophenotype biomarkers are a subtype of trait biomarkers that are based on links between genes and specific depressive phenotypes (Hasler et al., 2004). They are permanent, cosegregate with the disorder within families and are present at a higher rate in affected families than in the general population (Beauchaine, 2009; Fox and Growdon, 2004).

The benefits of having an aetiologically-sound and objective panel of biomarkers for depression are significant: (1) their presence can be used to predict probability of onset or presence of the disorder, (2) they can be used to stratify the disorder according to severity and symptomatology, (3) they can be used as an indicator of disease prognosis and (4) they can be used to predict response and track progress following a therapeutic intervention (Biomarker-Definitions-Working-Group, 2001). While the focus of this review is on molecular biomarkers of depression, it is important to recognise the existence of other behavioural and environmental factors which can predict or influence prognosis as well as treatment response (Branchi et al., 2013; Harmer, 2008; Trivedi et al., 2006, 2011). In any case, validated biomarkers would also provide a much needed deeper understanding of the neurobiology of depression to facilitate the development/refinement of