Advances in Stem Cells Biology: New Approaches to Understand Depression

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Abstract Depression is a highly prevalent complex neuropsychiatric disorder, which ranks first among all mental and neurological disorders as a contributor to the global burden of disease. However, available treatments are still far from ideal, for their specificity as well as their efficacy. This situation can now be improved by the increasing availability of stem cells, which allows the development of in vitro human neural systems to model the brain. These models complement observations from animal models and patients with depression, allowing for a better understanding of the complexity of this psychiatric illness and potential treatments. Cells derived from the olfactory neuroepithelium, multipotent fetal hippocampal progenitor cells (HPCs) and human induced pluripotent stem cells (iPSCs) have shown promising leads. Using HPCs and iPSC-derived forebrain neurons, we managed to provide further insights into the action of drugs with antidepressant action as well as on molecular mechanisms underlying the effect of stress and inflammation, both linked to the pathophysiology of depression. Particular attention has been paid to the complex pathways by which the immune and stress systems differently determine the final developmental fate of HPCs and the synaptic plasticity of iPSCs. The combination of accessibility and validity of the available stem cells models will allow further work to increase our insights into the biology of depression and support the identification of novel therapeutic targets.

Introduction

How Can We Best Study Depression?

Depression ranks first among all mental and neurological disorders as a contributor to the global burden of disease and causes a heavy load on patients and their

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families. However, available treatments are far from ideal. Only a third of patients respond to the initial treatment, another third will get better only after several changes of medication and the rest will go on to be treatment resistant (Rapaport et al. 2003; Trivedi et al. 2006). Why is this? We still do not know why depression happens; neither do we clearly understand how antidepressants work. Much of the current understanding about the pathogenesis of major depression has come from animal models (Krishnan and Nestler 2011) as well as from peripheral (Felger et al. 2012) and central nervous system (CNS; Raison et al. 2010) circulating measurements from patients with depression. Due to the unique and complex features of human depression, the generation of valid and more insightful depression models has been less straightforward than modeling other disabling diseases (Krishnan and Nestler 2011). One possible approach is that of focusing on brain models, using neural cell lines. Undifferentiated or differentiated tumor-derived cells have been used as a translationally valid experimental model for several psychiatric disorders, including depression (Donnici et al. 2008; Alboni et al. 2013). However, such lines are limited in the cell types they can be made to resemble and may have major chromosomal abnormalities (Bray et al. 2012). Into this breach come new brain models of neural stem cells. Using multipotent fetal hippocampal progenitor cells (HPCs) and human induced pluripotent stem cells (iPSCs), we have mimicked clinically pertinent conditions to depressive disorders by combining depressogenic insults and antidepressant strategies (Anacker et al. 2011b, 2013a, b; Zunszain et al. 2012; Horowitz et al. 2015). Indeed, our outcomes provided evidence for the efficacy of such models in understanding the disorder as well as for giving more insights into antidepressants and their mechanisms of action. Particularly, we focused on neurogenesis as a potential candidate mechanism for the etiology of this condition as well as a substrate for antidepressant action.

The Neurogenesis Theory of Depression

A reduction in hippocampal neurogenesis, that is the birth of neurons from stem cells, has been suggested as one of the neurobiological alterations mediating the development of depressive-like behavior in animals, particularly under conditions of stress (David et al. 2009; Snyder et al. 2011; Surget et al. 2011). In the absence of effective neurogenesis, the depressive-like behavior elicited in animals by stress includes the hallmark abnormalities of clinical depression: increased hypothalamic-pituitary-adrenal (HPA) axis activity, glucocorticoid resistance (that is, impaired suppression of HPA axis activity by dexamethasone), anhedonia (assessed using the sucrose preference test), and behavioural despair (assessed using the forced swim test) (David et al. 2009; Snyder et al. 2011; Surget et al. 2011). Moreover, it has been suggested that an impaired neurogenesis may also precipitate depressive

symptoms because of the lack of neurogenesis-dependent cognitive functions, such as the ability to enhance encoding of new memories and responding to contextual changes, which may be protective against behavioural despair in the face of repeated stressors (Sahay et al. 2011). Recent studies showing that the magnitude of adult neurogenesis in humans is probably larger than generally believed (Snyder and Cameron 2012; Spalding et al. 2013) provided even stronger support for the importance of neurogenesis and its proposed involvement in the association between stress and depression (Snyder et al. 2011).

Increased inflammation can also cause reductions in neurogenesis. Immune molecules, including interleukin-1beta (IL-1β), IL-6, interferon-alpha (IFN-α) and tumor necrosis factor-alpha (TNF-α) have been shown to be significantly upregulated in the peripheral blood of depressed patients (Howren et al. 2009; Dowlati et al. 2010). Particularly in the context of depression, IL-1β, IL6, IFN-α and IFN-γ have also been shown to easily move from the periphery into the brain (Dantzer et al. 2008; Najjar et al. 2013). Once they cross the brain-blood barrier, these molecules can alter distinct molecular and cellular mechanisms, including cell proliferation and neuronal maturation (Pickering and O'Connor 2007; Alboni et al. 2014) associated with complex cognitive processes, such as mood and learning functions (Makhija and Karunakaran 2013; Shigemoto-Mogami et al. 2014). In particular, using animal models, IL-1β, IL-18, IFN-α and TNF-α, have been shown to contribute to inhibition of synaptic plasticity and memory consolidation (Pickering and O'Connor 2007), causing similar impairments to those often reported in patients with major depressive disorder or in experimental models of depression (Pollak and Yirmiya 2002; Capuron and Miller 2004; Zunszain et al. 2013).

Furthermore, stress and inflammation interact. For example, in response to chronic IFN-α administration, patients with Hepatitis C Virus showed a hyper-reactivity of the HPA axis (Capuron et al. 2002; Raison et al. 2010). Most interestingly, around 30 % of those patients developed clinically significant depression (Raison et al. 2009), strengthening the notion that stress and inflammation might be among the crosstalk pathways leading to the pathogenesis of the depressive disorder. Indeed, it is of relevance in this context that stress and inflammation are among the different downstream molecular mechanisms that distinct antidepressants activate. Particularly, antidepressants from the selective serotonin reuptake inhibitor (SSRI) class, such as fluoxetine, have shown to normalize stress-induced HPA hyperactivity in rodents (Perera et al. 2011; Surget et al. 2011), whereas other serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants, such as venlafaxine, have normalized inflammatory alterations in cytokine-treated depressed patients (Capuron et al. 2002). However, irrespective of which distinct downstream molecular mechanisms specific antidepressants activate, those pathways may ultimately converge to stimulate neurogenesis, which is proposed as an essential substrate for antidepressant action (Schloesser et al. 2010).
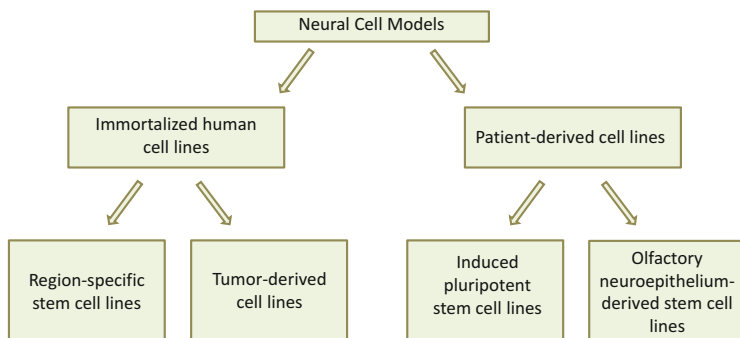
Fig. 1 The different range of neural cell models used to study depressive disorder and mechanisms of action of antidepressants

Experimental Approaches

Among the approaches available to investigate the complexity of depressive disorders, immortalized cell lines and patient-derived stem cell lines have proved to be relevant in vitro human neural cell models (Fig. 1). Immortalized cell lines allow molecular, developmental and pathophysiological mechanisms to be studied with considerable reliability. Examples of immortalized cell lines are region-specific neural stem cells and tumour-derived cells. An alternative cell-based approach is to derive and compare neural cells from patients and control individuals, particularly using iPSCs or olfactory neuroepithelium-derived cell lines. Indeed, the use of cells from patients allows a more attentive analysis of the pathological processes arising from the whole range of genetic susceptibility variants characterizing each individual (Srikanth and Young-Pearse 2014). Evidence has shown the significant incidence of distinct genetic polymorphisms in patients with psychiatric conditions, including depression (Cao et al. 2015; Chen et al. 2015; Wang et al. 2015), suggesting the importance of using such models to investigate genetic differences, which may allow for a predictive diagnosis of this disorder (Pasca et al. 2014). For the purpose of this chapter we will focus on immortalized stem cells and iPSC models. We will subsequently report our findings, providing evidence for their efficacy in understanding depressive disorders and antidepressant mechanisms of action.

Immortalized Human Neural Cell Lines

Neural Stem Cell Lines

Stem cells derived from human fetal brain are multipotent (i.e., they can give rise to a range of neurons and glia) and allow developmental and physiological processes

to be studied more faithfully. Particularly, clonal neural stem cell lines can be generated by conditional immortalization, whereby a regulated gene that drives cell division is introduced into the cell's genome, allowing controlled expansion and differentiation (Pollock et al. 2006). Indeed, neural stem cell lines with normal chromosomes have been established from several human fetal brain regions, including cerebral cortex, hippocampus and striatum. This approach has several unique advantages. First, it delivers data from living human brain cells, not easily accessible in clinical samples; second, it can mimic a multitude of clinically relevant conditions within a tightly controlled experimental environment, providing a model system with which to explore the mechanisms of drug treatments for a variety of psychiatric disorders; and finally, it generates findings that are directly translatable in clinical samples (Bray et al. 2012). Using this approach, we have modeled "depression in a dish" using the cell line HPC0A07/03C (provided by ReNeuron Ltd, London), derived from the hippocampus, which allowed us to translate findings from bench-to-beside-and-back (Anacker et al. 2011b, 2013a, b; Zunszain et al. 2012; Horowitz et al. 2015). We will describe our observations in further detail.

Modeling the Role of Stress

As a first example of our translational approach, we managed to provide evidence for the detrimental role of stress on hippocampal neurogenesis. Impaired neurogenesis in rodents has recently been shown to contribute to the development of depressive-like behaviours, including anhedonia and behavioural despair in response to acute and chronic stressful insults (Zhu et al. 2014). Using our human hippocampal model, we showed that cortisol caused a reduction in the generation of new neurons via glucocorticoid receptor (GR)-dependent mechanisms, an effect which could be fully reverted by treatment with the SSRI sertraline. Indeed, subsequent stimulation with a GR-antagonist completely abolished the increase in neurogenesis induced by the antidepressant (Anacker et al. 2011b). Our model proved to be effective in providing further details from the complex interaction between stress and neuronal generation, proposing GR-dependent mechanisms as possible future targets of antidepressant drug treatment to overcome neurogenesis-related disturbances in depression (Anacker et al. 2011a).

Modeling the Role of Inflammation and Oxidative Stress

As a second example of the use of our model, we demonstrated the involvement of inflammation on hippocampal neurogenesis. Previous evidence had reported that in vitro stimulation with distinct cytokines, including IL-1β, IL-6, IFN-α and TNF-α, caused a significant alteration in both proliferation and neuronal maturation of human and animal cells (Borsini et al. 2015). Using our in vitro human neuronal model, we investigated the effect of two pro-inflammatory cytokines, IFN-α

(our unpublished observation) and IL-1β (Zunszain et al. 2012), on neurogenesis. Findings showed that, upon treatment with both cytokines HPCs developed a "depressive phenotype" comprising reduced neurogenesis. Moreover, IL-1β was responsible for alterations in transcription pathways regulating the metabolism of tryptophan. Indeed, the inhibitory effects of IL-1β on neurogenesis were mediated, at least in part, by activation of the neurotoxic branch of the kynurenine pathway, one of the main pathways postulated to be involved in the development of depressive disorders (Baranyi et al. 2015).

A third example involved the use of tert-butylhydroxiperoxide (TBHP) to model oxidative stress. High levels of reactive oxygen species, shown in depressed patients, are known to affect cellular constituents, leading to neoepitopes and damage-associated molecular patterns that promote further immune responses (Bakunina et al. 2015). Cells treated with TBHP showed a dose-dependent increase in lipid peroxidation as well as reduced cell viability.

Studying Mechanism of Action of Antidepressants

Finally, we used this model to investigate the immunomodulatory properties of distinct compounds with antidepressant actions. We explored the effects of several conventional monoaminergic antidepressants and the omega-3 polyunsaturated fatty acids (n-3 PUFAs), eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), on HPCs treated with the inflammatory and depressogenic IL-1β. In contrast to sertraline and DHA, which had pro-inflammatory properties, venlafaxine and EPA were shown to have anti-inflammatory effects via decreasing distinct cytokines, including IL-6, IL-8 and IP-10 (Horowitz et al. 2015). In addition, these compounds showed differential effects on neurogenesis. Again, the findings demonstrate the efficacy of this model for studying specific mechanisms of action of drugs with antidepressant action.

Tumour-Derived Cell Lines

These lines, with an ability to expand quite readily in culture, provide a standardized and potentially limitless alternative to study intracellular mechanisms of antidepressant action. Currently, the most commonly used human neural cell line is SH-SY5Y. This line displays neuronal properties, including neurite outgrowth, neurotransmitter synthesis and relevant receptor expression. The SH-SY5Y line has been widely used to study intracellular mechanisms of different antidepressant action, including the SSRI sertraline, the selective norepinephrine reuptake inhibitor (SNRI) desipramine and the norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion (Lin 2015).

Patient-Derived Neural Cells

IPSCs

Among the patient-derived cell models, iPSC technology provides distinct cell types that are considered to be central to psychiatric disorders, such as those of the cortex and the hippocampus (Jaworska et al. 2015). Indeed, primary somatic cells, typically from skin, can be taken from an individual and reprogrammed into pluripotent stem cells that can give rise to all of the cell types that characterize the body, including those of the CNS. By capturing a patient's entire genome and any possible epigenetic variations, iPSCs constitute a unique source of material for studying neurodevelopmental features of psychiatric disorders in vitro.

Reports are now beginning to emerge in which this technology has been applied to cells taken from psychiatric patients. For example, human keratinocytes from healthy controls and patients with bipolar depression have been reprogrammed into cortical neurons. When compared with control cells, neurons derived from patients with bipolar depression showed an alteration in the expression of transcripts that regulate Hedgehog signaling (Cheung et al. 2009), as well as modulations in key components of the mTOR pathway (O'Shea and McInnis 2015), which have both been shown to be among the mechanisms involved in the development of depressive disorders (Rajendran et al. 2009; Ignacio et al. 2015). Using iPSC-derived forebrain neurons, we showed that ketamine, known to have fast-acting antidepressant efficacy in treatment-resistant patients, was able to rescue the detrimental effects produced by treatment with IL-1β and to increase the number of presynaptic and postsynaptic proteins.

Olfactory Neuroepithelium-Derived Stem Cells

Cells from the olfactory mucosa, which can be extracted through biopsy, can easily propagate, forming neurospheres of neural stem cells and differentiating neural progenitor cells. Although there are no studies using olfactory neuroepithelium-derived cells from depressed patients, they have been used to study schizophrenia (Matigian et al. 2010; Fan et al. 2012), suggesting the importance of using such models to investigate genetic differences, which may allow for a predictive diagnosis of depression in certain individuals.

Conclusions and Limitations of the Cell Models

Stem cell-based approaches to study psychiatric disorders are advancing on two main fronts. On one hand, clonal cell lines which accurately model the CNS are being used in controlled experiments to assess the mechanisms of antidepressant

action for psychiatric disorders, which might in the short term lead to advancements in therapeutic strategies for these conditions. On the other hand, patient-derived cells and cells from control patients allow the study of pathological processes deriving from the multiple genetic susceptibility variants, which can now be investigated with more accuracy. However, both cell models have some limitations that need to be pointed out. Although human neural cell lines can be used to investigate the molecular and cellular functions of individual susceptibility genes, they do not capture the many genetic variables that contribute to the development of psychiatric disorders (Bray et al. 2012). Patient-derived cell lines offer the advantage of capturing each individual's whole genome, but there is limited knowledge as to which cell types are most relevant to study specific psychiatric conditions (Sandoe and Eggan 2013). In addition, while iPSC technology can model the effects of medications, these cells may lose the effects of environmental influences that may contribute to the development of the psychiatric illnesses, such as stressors or negative life events (Okano and Yamanaka 2014).

Although cell-based models are still unable to elucidate the molecular complexity of psychiatric illnesses, the enormous progress in stem cell technologies has revolutionized the field of "in vitro disease modeling," providing not only a window into the mechanisms underlying the depressive disorder but also a platform for screening novel therapeutic strategies for the prevention and treatment of this condition.

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