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Review article

Regenerative medicine in Huntington's disease: Strengths and weaknesses of preclinical studies

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ABSTRACT

Huntington's disease (HD) is an inherited neurodegenerative disorder, characterized by impairment in motor, cognitive and psychiatric domains. Currently, there is no specific therapy to act on the onset or progression of HD. The marked neuronal death observed in HD is a main argument in favour of stem cells (SCs) transplantation as a promising therapeutic perspective to replace the population of lost neurons and restore the functionality of the damaged circuitry. The availability of rodent models of HD encourages the investigation of the restorative potential of SCs transplantation longitudinally. However, the results of preclinical studies on SCs therapy in HD are so far largely inconsistent; this hampers the individuation of the more appropriate model and precludes the comparative analysis of transplant efficacy on behavioural end points. Thus, this review will describe the state of the art of *in vivo* research on SCs therapy in HD, analysing in a translational perspective the strengths and weaknesses of animal studies investigating the therapeutic potential of cell transplantation on HD progression.

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1. Introduction

Huntington's disease (HD) is an inherited neurodegenerative disease with a prevalence of 5–10 cases per 100,000 people worldwide (Ross and Tabrizi, 2011) characterized by cognitive and psychiatric impairments and involuntary choreiform movements. The most common onset is around the age of 40 (although approximately 5% of cases have juvenile onset), with average life expectancy duration of 15 years. The mutation causing HD consists of an abnormal expansion of CAG-encoded polyglutamine repeats (from 36 to 121 repeats) in the gene codifying for the protein huntingtin (*HTT*). The length of the CAG repeat is inversely correlated with the onset of clinical symptoms (Duyao et al., 1993; Zoghbi and Orr, 2000). Therefore, the higher and the lower number of CAG repeats result in early and later in life onset of disease, respectively. Moreover, patients with higher numbers of CAG repeats show a more rapid progression of disease. However, although the length of the CAG repeat is crucial to determine HD onset and severity, clinical expression can be modulated by modifiers such as environmental and other genetic factors.

The most striking neuropathological hallmark of HD is the atrophy of GABA medium spiny neurons (MSNs) in the striatum as seen by post mortem histological evaluation, but several cerebral regions also show signs of neurodegeneration as the disease progresses (Rosas et al., 2003). The mechanisms underlying neurodegeneration in HD are not totally elucidated. Several hypotheses based on experimental and clinical evidence have been advanced, including decreased cortical levels of Brain-Derived Neurotrophic Factor (BDNF) (Zuccato et al., 2011; Zuccato et al., 2010), abnormal immune activation and neuroinflammation (Crotti and Glass, 2015), impairment of mitochondrial function (Zuccato et al., 2010). Preclinical studies performed on animal models of HD have provided valuable information on physiopathology of the disease. These models have been also exploited to identify therapeutic targets and develop interventions, but currently there is no effective therapy to delay the onset or to slow the progression of HD: the majority of therapeutic strategies attempt to reduce the severity of symptoms to improve the quality of life of the patients (Handley et al., 2006; Kumar et al., 2015). At present several novel therapeutics that may target the abnormal cellular processing triggered by mutant huntingtin (mHtt) are under intense investigation(Chopra et al., 2016; Thomas et al., 2008), although it is still difficult to translate these treatments to the clinics. The marked striatal atrophy observed in HD is a main argument in favour of cell replacement therapy, as it is unlikely that the extensive brain damage characteristic of this disease can be treated solely by drug-based therapies. To date efforts have been made to restore motor and cognitive functions by transplanting human foetal striatal tissue into the striatum of HD patients (Bachoud-Levi et al., 2006). Unfortunately, this therapeutic approach failed so far to re-establish lost functions in the long term; in addition, both ethical and practical issues have limited the use of human foetal striatal tissue (Bjorklund, 1993; Isacson and Breakefield, 1997). Thus, the use of renewable and expandable cells such as stem cells (SCs) might represent a promising therapeutic perspective for transplantation in HD patients.

Although we are still far from use of SCs in clinical settings, evidence from animal studies showed the partial reconstruction of neuronal circuitry and functional efficacy following cell transplantation in HD models (Dunnett and Rosser, 2007; Nakao and Itakura, 2000; van Dellen et al., 2001). In particular, three sources of SCs such as neural SCs (NSCs), mesenchymal SCs (MSCs) and pluripotent SCs (PSCs) have been tested to date in HD animal models.

The aim of the present review is describing the state of the art of *in vivo* preclinical research on cell therapy in HD, and to analyse in a translational perspective the strengths and weaknesses of rodent models in the investigation of the therapeutic potential of cell transplantation. As HD has a monogenic aetiology with well-defined neurological symptoms, the modelling of the disease in animal models is apparently simpler than for other complex neurodegenerative diseases with a largely sporadic origin (i.e. Alzheimer's disease). In point of fact, in the case of HD a variety of rodent models are available that mimic various forms of the pathology recapitulating, at least in part, neuropathological features and symptoms of human HD. Furthermore, the behavioural phenotype of both transgenic and chemical models of HD has been thoroughly characterized, including longitudinal follow-up of disease progression, hardly achievable with HD patients. All this considered, it is somewhat surprising that the knowledge so far attained on HD pathophysiology through the study of rodent models has not been exploited in the assessment of innovative treatment efficacy. As we will show below, the results of preclinical studies on SCs therapy in HD are so far largely inconsistent: different kinds of SCs have been tested in different rodent models applying diverse experimental designs, and this hampers the individuation of the more appropriate model and a comparative analysis of transplant efficacy on behavioural end points. We suggest that an integrated *in vivo* approach, which is able to associate longitudinal and fine-grain analysis of different behavioural domains together with detection of morphological and molecular changes in models mirroring different though substantial aspects of HD pathology, might support the evaluation of the functional efficacy of SCs therapy.

2. Huntington's disease: a complex symptomatology from a single gene

HD is clinically characterized by a triad of emotional, cognitive and motor alterations, but the onset of HD is defined by the occurrence of motor symptoms. Chorea, a dance-like involuntary movement, is the clinical hallmark of HD that gives the name to disease, present in more than 90% of individuals (Koutsis et al., 2014). Chorea consists of an unpredictable jerking of all the parts of body, whose severity can be worsened by stress and psychiatric disorders. As the disease progresses, impairment of voluntary movements occurs including bradykinesia, gait abnormalities, reaching behaviour and manual dexterity (David et al., 1987).

Cognitive impairments and psychiatric manifestations can be detected many years before motor diagnosis (Duff et al., 2007; Epping et al., 2016). Deficits of different cognitive processes including executive function, visuo-spatial abilities, memory, attention and language are involved depending on disease progression (Ho et al., 2003; Lawrence et al., 1999; Paulsen and Conybeare, 2005; Schmidtke et al., 2002). Psychiatric symptoms may include depression, anxiety, impulsivity and irritability (Berrios et al., 2002; Kirkwood et al., 2002; Kloppel et al., 2010; Witjes-Ane et al., 2002). Depression is common, reported in over half of patients also before the onset of the earliest cognitive changes (Paulsen et al., 2005). Cognitive and behavioural alterations are most highly associated with functional decline, interfering with daily activities and autonomy of HD patients.

The main neuropathological hallmark of the disease is the marked atrophy of the striatum, due to preferential loss of MSNs, with relative sparing of interneurons. However, neuronal loss has been identified in many other regions of the brain, including the cerebral cortex (Rub et al., 2016). Although the striatal pathology is accountable for core symptoms of HD, the clinical heterogeneity and complexity of HD can be explained better by cortical involvement (Rosas et al., 2008).

From the identification of the HD gene (MacDonald et al., 1993), various hypotheses have been postulated on the potential role of mHtt in HD pathology. The gain of function model has supported