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Editorial

Human Motor Neuron Obtained from iPSCs of the Peripheral Blood as the Most Promising Tool to Define Pathomechanisms and Novel Therapies in ALS

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Editorial

Difficulty of translation from preclinical to clinical settings represents the main limitation in deciphering pathomechanisms of neurodegenerative diseases, and this is primarily due to the shortage of adequate pre-clinical models. This is especially true for Amyotrophic Lateral Sclerosis (ALS). Due to the absence of naturally occurring ALS in rodents, informative transgenic mice are the most frequently used animal models [1]. However, albeit they have been useful for studying some pathological mechanisms of the disease, none of them perfectly replicate the human ALS. Developmental, and anatomical differences between mice and humans may explain the gap in translation. Several cellular models are also available such as neural cell lines [2-4]. However, as cell lines are mostly tumor-derived and have become immortalized, they may display significant biological differences from neuronal cells. Primary neuronal cultures would be therefore the most appropriate *in vitro* model, but the major problem is that mature neurons have limited proliferation capacity. As a matter of fact, motor neurons (MNs) have been isolated by immunomagnetic separation by our group [5], demonstrating some survival potential in serum-free media in defined biochemical conditions. The induced pluripotent stem cells (iPSCs) [6] represent a breakthrough in stem cell field. These cells may be generated using several delivery systems [7,8] and certainly present numerous advantages compared to other pre-clinical approaches, allowing the generation of patient specific models able to reproduce the disease phenotype. iPSCs, unlike tumor cell lines, are primary cells but with an unlimited proliferation capability. They can be generated from any patient and can be differentiated into any cell type. In ALS, iPSCs-derived MNs may be obtained from both patients harboring genetic mutations linked to the disease (such as SOD1, TARDBP, FUS and C9ORF72) than from sporadic patients (the prevalent cases) without a disease family history. Beside their differentiation into MNs, iPSCs can generate other cell types that have been proved to have important implications in the disease, such as glial cells. Interactions between different neural cells can therefore be investigated *in vitro*. Albeit fibroblasts are most commonly used, several different starting cells have been reprogrammed and ideally, each dividing somatic cell may be used. In particular, peripheral blood cells present several advantages compared to other cell types: they can be easily obtained in a noninvasive way and they do not require prolonged culture before reprogramming avoiding possible genetic alterations [9]. Clinical, genetic and phenotypic heterogeneity of ALS may also lead to multiple and discordant responses with analogous treatment. Another important advantage using iPSCs, is the possibility to use cells from patients still alive, allowing to design a patient specific therapy [10].

The reprogramming of somatic cells from ALS patients and their differentiation to MNs may represent a major achievement in understanding the mechanism of ALS, identifying innovative therapeutical strategies. As a proof of principle, iPSC derived MNs have been also utilized to start a clinical trial in humans after FDA approval [11]: if this approach is reproducible, other neurodegenerative diseases will definitely take great advantages from this innovative, unprecedented approach that may represent a paradigm shift for effective drug finding in ALS as in other neurodegenerative disorders. Indeed, thanks to the high versatility of iPSCs, these cells may also be differentiated into other neuronal cell types such as dopaminergic neurons. Two studies demonstrated that both transplantation of autologous iPSC-derived neural cells [12] or iPSCs-derived dopaminergic neurons from patients with Parkinson's Disease or from healthy donors [13], survived and functioned when transplanted in PD primate models and no tumor formation was observed. These preclinical studies, showing clear clinical benefits and graft survival

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of iPSCs-derived neuronal cells, strongly support the validity of this approach for cell replacement in neurodegenerative diseases, suggesting a further scenario for the peripheral blood derived iPSCs.

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