Advances in Bioscience and Clinical Medicine
ISSN: 2203-1413
www.abcmed.aiac.org.au

Review Article

Stem Cells and their Extensive uses in Multiple Medical Fields and Especially in Neurological Diseases

Dr. Lidia Sarnataro, MD, MS*

Corresponding Author: Dr. Lidia Sarnataro, MD, MS, E-mail: lidiasarnataro@gmail.com

ARTICLE INFO

Article history
Received: March 15, 2022
Accepted: June 25, 2022
Published: July 31, 2022
Volume: 10 Issue: 3

Conflicts of interest: None.
Funding: None.

Key words:
Stem cells and their classification, Regenerative medicine, microRNA, cell cycle, ESC, MSCs, iPSCs, Somatic stem cell, cancer stem cell, NSCs, EAE, Spinal cord injury, Osteoarthritis, tendon-bone insertion injuries, retinal progenitor phenotypes, IVH, PHH, Alzheimer's disease, Parkinson's disease, dental pulp stem cells, PARK2, Parkin expression, PINK1, Transcriptome analysis, Adhesive arachnoiditis, Arachnoid granulations (AGs), Idiopathic intracranial hypertension (IIH), Arnold Chiari malformation I (type I ACM), syringomyelia, Tarlov cyst.

ABSTRACT

Since they were first discovered and used in animal models in the 1950th, stem cells are assuming a key role in the research field. These types of cells are undifferentiated cells deriving from a single cell that is able of a clonal proliferation differentiating into different cells and tissues. It is possible to classify them into two main groups considering their main features. Moreover, speaking about stem cells, it is important to mention the key role of some small non-coding RNA molecules also known MiRNAs (microRNAs) in the cell cycle regulation. Generally, stem cells are very useful in cellular therapy helping the regeneration of entire organs. They also allow a deep understanding of development and pathogenesis of many diseases and are useful in drug development. In general, the aim of this article is to talk about stem cells and their uses in multiple medical fields and especially in neurological diseases. A comprehensive explanation of stem cell classification and miRNAs role in the cell cycle regulation of these cells in clinical application as well as gene alterations in some diseases is included. And finally, very interesting stem cell research will be also discussed. Unfortunately, studies on adhesive arachnoiditis, a rare neurological disease mostly associated to Tarlov cysts (TC), are still few. In addition, other associations between arachnoiditis and Chiari malformation, as well as syringomyelia and ACM, have been found. And, finally, association between idiopathic intracerebral hypertension and arachnoiditis granulations (AGs) were also demonstrated.

INTRODUCTION

Generally, such types of cells are undifferentiated cells deriving from a single cell that is able of a clonal proliferation differentiating into different cells and tissues.

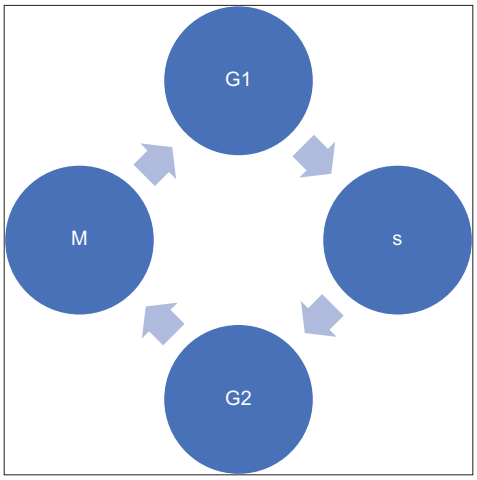
It is possible to find these cells in the different stages of life. In fact, even in adults, it is possible to find some of them in tissues with the aim to repair future injuries to that organ. This type of cells has some major characteristics such as self-renewal, clonality, and a differentiation potential, which are different among the cells going from the embryonic stem cells (ESCs) with a high self-renewal potential and potency to somatic stem cells with a low self-renewal chance and less potency. While ESCs origin from the blastocyst and can differentiate into specific tissues, some of the progenitor cells in organs do not differentiate completely and are able to proliferate in a second time either for self-renewal or after a trauma. There are also stem-like cells known as cancer stem cells (CSCs) that can lead to the initiation of a cancer type.

The first experiments with these cells began during the 1950s with a bone marrow transplantation in animal models. Since then, this therapy has been used to treat many blood disorders.

However, we have to say that this regenerative effect is a direct consequence of their produced molecules and especially growth factors, therefore the main goal would be to take advantage of these structures avoiding using the cells. We must consider that among the different types of stem cells just the adult stem cells can avoid ethical and legal issues. These cells can be found in all tissues of the body, and especially the adipose tissue-derived stem cells (ASCs) can be isolated from the subcutaneous tissue and their use is very encouraging in regenerative medicine.

Published by Australian International Academic Centre PTY.LTD.

http://dx.doi.org/10.7575/aiac.abcmed.v.10n.3p.1



Graphic 1. Cell cycle

Regenerative medicine is very important for treatment, and to study the etiopathogenesis of many diseases. Despite the many ethical issues in stem cell research, these cells have been very useful to many scientists to develop the tissue regeneration in many neurological as well other diseases (1).

To fully understand the cell cycle regulation, we must go back to the phases of the cell division, which are G1 as Gap 1, S as synthesis, G2 as Gap 2 and M as Mitosis like shown in the graphic 1 below.

Normally, in the Gap 1, there is a production of proteins for the DNA replication. In the S phase, DNA replication occurs, and in the G2 phase, the produced DNA is examined. And finally, in the Mitosis, the is the cell division. Afterwards, the produced cells are blocked into the G1 phase also known as G0 phase, that is very important for cellular homeostasis in term of ability to either block the proliferation or go back to the cell cycle and self-renew. Each of these phases is normally variable among different cells, being, for instance, longer in murine somatic cells and shorter in murine ESCs (mESCs). On the other side, human ESCs (hESCs) have a shorter G1 (3 h) than human somatic cells (10 h). Since G1 phase duration varies so much, it represents the key for cell determination. Exactly, it was found out that, in the G1 phase, there is a high level of a protein called cyclin D, that binds enzymes called CDK4/6 forming heterodimers. For instance, in this case, it is important to mention the genes known as E2F, that encode some transcription factors, that the RB uses as targets. On the other side, a RB tumor suppressor protein (pRb) regulates negatively these genes. When E2F transcription factors are hypophosphorylated, they block the cell cycle at the G1 phase. By hyperphosphorylation instead the transition into S phase occurs. This E2F/pRb activity is very important for ESCs progression. In general, a cyclin dependent kinase protein (CDK), and exactly a cyclin E-CDK2 complex and a cyclin B-CDK1 complex are responsible for the cell cycle regulation (2).

STEM CELL CLASSIFICATION

These cells can be divided into two main groups considering main characteristics such as origin and differential potential.

According to their origin, we can differentiate four categories of cells: embryogenic, fetal, adult and induced pluripotent stem cells (iPSC) (Table 1). Embryogenic stem cells (ESCs) origin from the blastocyst. In this case, it is important to mention that transcription factors such as Nanog and Oct4 can maintain them in an undifferentiated state. In these conditions, it is possible after freezing them to make further experimentations. However, embryonic fibroblast cells (MEFCs) or a medium containing the leukemia inhibitory factor (LIF) are needed to avoid the formation of typical embryoid bodies. On the other side, there are the adult stem cells present in differentiated tissues, such as Mesenchymal stem cells (MSCs) and human amnion epithelial cells, and they are anti-inflammatory and can ameliorate the repair injury in animal models. These autologous cells do not cause ethical controversies. The transplantation of adult stem cells has been proved to restore some injured organs. Moreover, cultured adult stem cells can help in repair producing molecules with many different properties. In this way, adult stem cells can renew and repair tissues after an injury. During ontogenesis, they are produced and then are dormant till local stimuli activate them. Normally, they can be found in an the so called “niche”, which is a special environment consisting of various signals from different mediators, where their self-renewal and differentiation is actively controlled. Following a symmetrical division, a stem cell will then produce identical daughter cells to repair damaged cells after injury. However, it is also possible an asymmetric division with an identical daughter cell and a differentiated daughter cell. Instead, the induced pluripotent stem cells (iPSCs) derive from genetically modified adult stem cells like ESCs. In 2007, Yamanaka and colleagues generated human iPSCs from adult human dermal fibroblasts using four factors called Oct3/4, Sox2, Klf4, and c-Myc. Since then, such cells are useful for the research. However, since the reprogramming factors are introduced using retroviral vectors and oncogenes like c-Myc, that can cause cancers, the use of these cells in a clinical study is limited. Safe methods have been investigated.

Their differentiation potential is important for a further differentiation into more 5 groups starting from totipotent or omnipotent and going through pluripotent, multipotent, oligopotent, and finally to unipotent (Tab. 1). Normally, totipotent, or omnipotent cells are very undifferentiated cells present in fertilized oocyte and can give origin to embryo and placenta. Pluripotent stem cells can instead differentiate into the 3 germ layers. As it was already mentioned above, iPSCs were created by Takahashi and Yamanaka and have similar characteristics to ESCs.

Multipotent stem cells differentiate from a single germ layer. The most important example of such cells is offered from mesenchymal stem cells (MSCs), that can differentiate into tissues derived from mesoderm such as muscle, bone, cartilage, adipose tissue, and into lung and neuronal tissue. The last one is an example of transdifferentiating because a cell from mesoderm can differentiate into ectoderm - neuronal tissue. Oligopotent stem cells can self-renew forming two or more cellular types in one tissue, such as, for instance, corneal and conjunctival cells in the ocular surface of the

Table 1. Stem cell classifications

Stem cells classifications					
Origin	**Embryogenic stem cells (ESCs)**	**Fetal stem cells (FSTs)**	**Adult stem cells (ASCs) or somatic stem cells**	**Induced pluripotent stem cells (iPSC)**	
Differentiation potential	Totipotent or omnipotent	Pluripotent	Multipotent	Oligopotent	Unipotent

pig, or myeloid and lymphoid cells, or also bronchiolar epithelium and alveolar epithelium.

Finally, unipotent stem cells can just differentiate into one cell type such as muscle stem cells or type I pneumocytes (1).

THE IMPORTANCE OF MIRNA IN CELL CYCLE REGULATION OF STEM CELL

MicroRNAs (miRNAs) are small non-coding RNAs. The first miRNA was discovered in 1993 and, until now, different miRNAs were described in plants, animals, and viruses. In humans, a number of 1881 miRNAs that can modulate the activity of many protein-coding genes in different phases of the cell cycle. Moreover, an alteration of their expression can lead to tumor formation and cardiovascular disease.

Normally, miRNAs are first transcribed in the nucleus as primary transcripts called pri-miRNA, that secondarily under the action of Drosha, RNaseII, endonuclease III, and Pasha/DGCR8 proteins give origin to pre-miRNAs. Then, it follows their transportation to the cytoplasm by Exportin 5, where they are transformed in double-stranded miRNA by Dicer and TRBP/PACT proteins. Additionally, the RNA-induced silencing complex (RISC) in the guided strand makes possible the interaction with a target mRNA (Figure. 1). In general, miRNAs are very important in cell cycle regulation in stem cells as well as in many other cells.

For example, ESCs have many miRNAs such as miR-290-295, miR-302, miR-17-92, miR-106b-25 and miR-106a-363 clusters, that can allow the progression in Dgcr8 knockout ESCs and the transition into the S phase, and control p21/Cip1 and cyclin E-CDK2 regulatory molecules. MiRNAs are also important in the cell cycle regulation in somatic stem cells and can also lead to the differentiation of specific hematopoietic lineages. However, there are issues about toxicity and delivery to solve before they can be used in patients.

As it was already mentioned above, mesenchymal stem cells (MSCs) are present in various tissues. In these cells, miRNAs such as MiR-16 and miR-143 can regulate their differentiation into specific cell types. An abnormal expression of pRB, p53, CDKs, CDKIs and cyclins can lead to cancer initiation and progression. Cancer stem cells (CSCs) lead to tumor formation, metastasis and chemoresistance. Transcriptional levels of many miRNAs are very different between the typical stem cells and these cells. For example, miR-17-92 cluster targets E2F-1 and cyclin D and can avoid apoptosis working together with the oncogene MYC. Let-7 is a very important miRNA for tumor progression and chemoresistance.

Downregulations of MiR-34a, b and c were demonstrated in many cancer cells such as lung, colon, and liver cancer. In addition, considering that a high expression of MiR-31 in liver cancer leads to a bad prognosis, it is possible to understand how it is inversely correlated with metastasis. MiR-15a/16 family has an important oncogenic role in chronic lymphocytic leukemia (CLL), but it is a tumor suppressor in a type of B cell lymphoma. If MiR-21 is upregulated, it can lead to some tumors such as lung, breast, pancreatic, brain and colon cancers. The overexpression of MiR-26a represents a negative oncological regulator in human liver cancer in vitro (2).

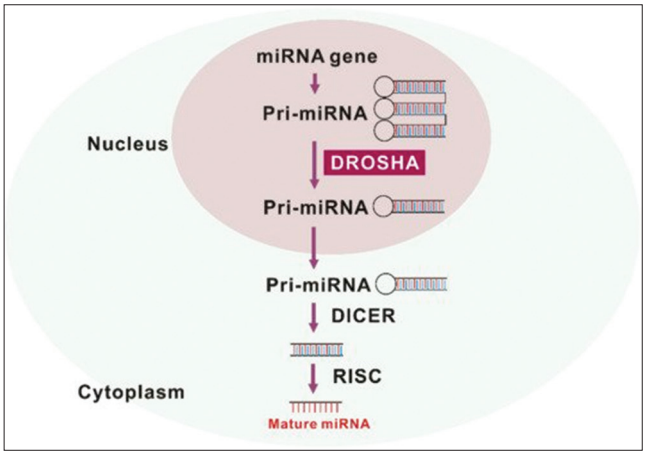


Figure 1. The maturation of miRNA by drosha ribonuclease III (DROSHA). Soo Jung Cho, et al. Drosha-Dependent miRNA and AIM2 Inflammasome Activation in Idiopathic Pulmonary Fibrosis. Int. J. Mol. Sci., 2020, 21 (5), 1668.

CLINICAL PRACTICE AND REGENERATIVE MEDICINE

In general, stem cells are very important in the clinical field and regenerative medicine. For example, ESCs have been used to study human development; iPSCs are critical for the investigation of new therapies, especially allowing to study the etiopathogenetic mechanisms and improving the treatment of many diseases such as diabetes mellitus, chronic myeloid leukemia, liver cirrhosis, Crohn's disease, heart failure, and neurological disorders. As it was already mentioned above, stem cells may also regenerate injured tissue or organs. However, immune rejection is still a problem, although mesenchymal stem cells, placental tissue and iPSCs have overcome this issue. Additionally, a genetic instability can produce different types of tumors. Especially teratomas and related tumors have been described in association with the application of embryogenic or IPSCs; and moreover, there are many ethical issues regarding ESCs because of the destruction of embryos (1).

In general, adult stem cells can differentiate into few specific cell lineages avoiding ethical and legal issues. Especially, adipose tissue-derived stem cells (ASCs), also called adipose-derived adult stromal (ADAS) cells, can be found in subcutaneous tissue and therefore are easy to use.

In an article of 2010 published by Farshid, et al (8.) in Clinical orthopedics and related research, it was demonstrated that ASCs have some characteristics of different cells and, therefore in particular conditions, can differentiate into one type of cells such as adipocytes, chondrocytes, osteoblasts, neuronal or muscle cells. For example, under low oxygen tension and particular growth factors or biomaterial scaffolds, it is possible to differentiate these cells in chondrocytes. Additionally, they can even be used to develop a biomaterial scaffold with mechanical properties like native cartilage.

As it was published by Yue Xu et Al (9.) in an article of 2021 in World J. Stem cells, many stem cells lineages can be used to heal the tendon-bone in tendon-bone insertion injuries after a reconstructive surgery. However, MSCs are the most promising cells to promote the healing.

Another disease, in which the stem cells are studied, is Osteoarthritis. Considering that the existing OA symptomatic treatments can't promote the regeneration of the degenerated cartilage or decrease the joint inflammation, embryogenic and induced pluripotent or mesenchymal stem cells can be used as injectable treatments in the Osteoarthritis joint cavity. However, research on mesenchymal stem cells is the most promising (10).

In general, umbilical cord mesenchymal stem cells are useful as allogeneic stem cell drugs in the injured tissue improving cartilage recovery and restoring healthy joints. However, more studies with randomized controls are still needed for the optimization of MSC therapy in osteoarthritis (11).

In many clinical trials, MSCs have been using for the therapy of inflammatory diseases, including Crohn's disease (12).

Stem cells research, innate immunity and microbiome are important to produce diagnostic tools such as biomarkers, for therapeutic uses, and even for prognostic measurements. In general, stem cells and their progenitors can be used for the etiopathogenesis and treatment of some gastrointestinal diseases (13).

Stem cell therapies have been also described in degenerative eye diseases. In fact, retinal progenitor phenotypes derived from embryonic stem cells/induced pluripotent stem cells and endogenous retinal stem cells can help to restore vision. Additionally, MSCs produce paracrine factors that can regenerate their axons in the degenerated optic nerve. Finally, NSCs can be a source of mediators of paracrine treatment and of replacement cells (14).

In cardiology, ESCs are found to be useful in treating myocardial infarctions through a cell replacement therapy, but some ethical and practical issues must be still solved before their clinical use (24). Especially, it would be very important to find the best cell type and the most effective way to prepare cells and avoid adverse effects (15). Embryonic and adult stem cells can also be used in tissue engineering in urology (25).

STEM CELLS IN NEUROLOGICAL DEGENERATIVE AND INFLAMMATORY DISEASES AS WELL AS IN SPINAL CORD TRAUMA

Stem cells therapy has been applied in many neurological degenerative diseases such as Alzheimer's and Parkinson's as well as in neurological inflammatory conditions, such as multiple sclerosis. Moreover, many studies on spinal cord injuries were conducted. Unfortunately, this promising cellular therapy has not yet been studied in arachnoiditis.

Extensive research about the above-mentioned diseases will be discussed in detail below.

PARKINSON'S DISEASE

Since the 1980s, stem cells experiment for PD with have been conducted. The result was that the transplanted fetal dopaminergic cells from the ventral mesencephalic tissue of fetuses survived improving the symptoms, but many patients had a sever dyskinesia maybe due to an excessive dopamine production and release. Later, the attention was focused on the discovery that embryogenic and adult stem cells can also differentiate in dopaminergic cells (22).

Since 2004 many articles about stem cells therapy in Parkinson's disease have been published.

As PD is a progressive, neurodegenerative disease caused by loss of the dopaminergic neurons in the substantia nigra. This leads to many motors and nonmotor symptoms and amongst them respectively dyskinesia and psychosis, both responsible for the dramatic reduction of the quality of life in affected patients. Medical treatments for the psychosis as well as nonpharmacological approaches and a dementia treatment have been used to reduce the symptoms and improve patient's life (21).

Then NSCs have also been studied and can differentiate into neurons, astrocytes, and oligodendrocytes. In laboratory, it was possible to generate a F3 human NSC line that was genetically modified to produce L-DOPA. These cells were transplanted into rat striatum and helped the host cells to survive against a neuronal injury. Then, they were administered intravenously in rat stroke models and were able to migrate into ischemic lesions and differentiate, improving the deficits. Even human derived bone-marrow MSCs can differentiate into neurons, and this makes them become promising in neurodegenerative diseases (23).

Although many therapies can improve the symptoms, until now, despite the extensive studies conducted on this, there is not a therapy that can block the disease progression. However, neural crest coming from dental pulp stem cells (DPSC) are considered now very advantageous in AD in comparison to the more studied bone-marrow derived MSCs (26). In younger patients, the cell replacement therapy had more beneficial outcomes. In fact, in a study, a transplantation of a type of human stem cells known as hVM1 clone 32 cells was performed in middle-aged mice with PD showing a prevention from motor and nonmotor impairments. However, considering that PD is a multifactorial disease, new approaches should focus on dopamine and nigrostriatal lesions (27).

There are many etiological factors contributing to the development of PD, and the most common are PARK2 mutations. In Northwest India, a genetic screening conducted from 2001 to 2006 on 120,000 patients of the UK Parkinson disease society brain bank clinical diagnostic criteria (UKPDBBC) was done. The result was that a high frequency of PARK2 together with a reduced Parkin expression leads to PD (28).

Moreover, in another clinical study, a gene mutation such as the PARK2 was found in 10% of the patients and is associated with a younger onset, severe symptoms, and a longer disease duration than in PD patients with unknown gene mutations. For disease modeling, iPSCs are very useful. In an experiment, neural progenitors and terminally differentiated neurons were derived from iPSCs lines from three healthy donors and three PD patients. At the end, a comparative transcriptome analysis of all patients was conducted to demonstrate how PARK2 can contribute to the pathogenesis (29).

As UC-MSCs show a neuroprotective effect in PD, a study was conducted to try to understand the mechanism behind it. An intranasal administration of these cells was used. The result was, on one side, reduction of locomotor symptoms and inhibition of the neuroinflammation saving the dopaminergic neurons, and, on the other side, alteration of the gut microbiota composition and modulation of the dopamine level in striatum and 5-hydroxytrypamine in the colon. In addition, these cells reduced some cytokines such as TNF-α and IL-6 and the conversion of NF-κB in the colon. Finally, the bacterial invasion of the epithelial cells as well as the degradation of fluor benzoate and the invasion of a pathogenic E. coli were reduced. In general, this demonstrates a neuroprotective effect of these cells in the brain through regulating intestinal microorganisms (30).

However, since the etiology of Parkinson is still not completely understood, the role of a biallelic mutations in the phosphatase and tensin homolog induced putative kinase 1 was studied as a possible cause for this disease. Exactly, differences between PINK1-patients and a control group were analyzed. In the experiment, the PD derived cells showed features such as an imbalanced proliferation and apoptosis as well as the reduction of the differentiation to tyrosine hydroxylase positive (TH+) neurons. The correction of this mutation could reverse the differentiation type. Moreover, the PD phenotypes in patient neuronal cultures and brain organoids showed an improvement after a therapy with 2-hydroxypropyl-β-cyclodextrin (31).

ALZHEIMER'S DISEASE

Since one of the first articles about vector systems for in vivo targeted delivery of genes and a suitable stem cell transplantation for Alzheimer's disease was published in 2004, the research in this field has been developing constantly (32).

Alzheimer's disease is a type of dementia and, in USA, represents the sixth cause of death. It is a progressive neurodegenerative disease responsible for memory loss and behavior impairments that leads ultimately to death. Stem cells therapy is very promising and especially MSCs have been studied till now. Despite good results in preclinical studies in AD animal models, clinical trials are limited (33).

Even if the two most important hallmarks of these diseases are an extracellular amyloid plaque and an intracellular neurofibrillary tangle, the AD pathogenesis is still not well understood. A neuroinflammation was shown to play a central role in cumulative studies in the development of the disease. The microglia is the most important player in the inflammation and different theories for the etiopathogenesis have been proposed. Even if the MSCs are a promising treatment, a limitation is their short survival in the host and the fact that, when these cells are administered intravenously, they are trapped in the spleen and lungs. They work through a paracrine effect secreting neurotrophic and angiogenic factors. In this way, they can enhance the microenvironment promoting the repair of the neurons in the damaged area. An intranasal administration of the secretome from these cells may lead to a memory recovery.

Moreover, these cells can modulate the neuroinflammation. In recent studies, a disbalanced endogenous neurogenesis and a loss of neural stem cells in adult hippocampus neurogenic areas were demonstrated. For this reason, a transplantation of MSCs can replenish these cells and stimulate the neurogenesis. After a transplantation of adipose tissue derived MSCs in APP/PS1 mice models, the neurogenesis in SVZ and SGZ hippocampal regions increased. These mesenchymal stem cells can also transfer their mitochondria to save dying neurons (Hayakawa, et al, 2016). More mechanisms include improving autophagy, decreasing ROS, renormalizing BBB and NVU. In China, a trial for the treatment of mild to moderate AD patients (NCT04388982) a nasal inhalation of exosomes of allogeneic adipose-derived mesenchymal stem cells is being used. In general, in the future, it will be very important to use genetic engineering of stem cells for stronger neurotrophic and immune-modulatory effect, biological scaffolds and vesicles for a targeted delivery (34).

In 2017, Duncan, et al (16) published an article in Stem Cell Research and Therapy about stem cell therapy in Alzheimer's Disease. As this illness is driven by an accumulation of β amyloid (Aβ) protein fragments in the brain, many pharmacological therapies, including vaccination, have already been developed to try to enhance the clearance of this protein as well to block its production through inhibition of the secretase, but the outcomes are not promising. However, even activated microglia in early stages and producing cytokines contribute to a neuroinflammation and leads to a loss of neurons and synapsis especially in the temporal lobes starting from the hippocampus and later progressing to most of the cortical layers. Since stem cell therapy has the aim to target the hippocampus, which is the very first part of the brain involved, it represents a new approach in fighting this disease. To do this, many different stem cells are being used such as ESCs, MSCs, NSCs and iPSCs. There are many theoretical approaches on their use. The first one is an endogenous repair upregulating the hippocampal neurogenesis through stimulation of the growth factors, but, unfortunately, this approach shows many weaknesses, since the neurogenesis in adult brain decreases with age and the neuronal loss is very high in AD and the hippocampal neurogenesis does

not affect other neurons to avoid its progression. Secondly, it comes an exogenous cell therapy through the transplantation of stem cells to introduce neuroprotective factors. Unfortunately, ESCs present a high risk of uncontrolled cell growth and ultimately tumor, so they cannot be used. The NSCs showed a good capacity to increase the neurogenesis and synaptogenesis, as well as to decrease the neuroinflammation and reverse the cognitive deficits, although a limiting factor is the generation of non-neuronal glial cell types.

MSCs are the most promising cells because they can be administered intravenously and can pass the blood-brain barrier reaching the brain and differentiate in neuronal cells capable of reducing amyloid plaques and stimulate neurogenesis, synaptogenesis, and neuronal differentiation. Finally, iPSCs can differentiate in dopaminergic neurons, can be useful in ischemic stroke and, after transplantation in the hippocampus, are able to differentiate in cholinergic neurons. They have a limited use for neuro-replacement in AD, but they can find a good application in the study of etiopathogenesis and drug screening. Moreover, they represent an important subject of study in vitro. Actually, a new clinical trial has started to evaluate the efficacy and safety of intracranially injected umbilical cord allogenic human blood-derived MSCs (Trial identifier: NCT01297218, NCT01696591). Nine AD patients were enrolled and Mini Mental State examination and the presence of Aβ pathology in the PET were the admission criteria. The patients were divided into two groups: those with a low dose (3×106 cells; $n=3$) and those with a high dose (6×106 cells; $n=6$) and had a MSCs injection into the hippocampus and precuneus. In a follow-up after 3- and 24-months, they did not show adverse reactions and any progression of the cognitive decline. However, there were not evident changes to AD pathology, showing that the neuroprotective effect described in animal models was not present. Later, other two trials (Trial identifier: NCT02912169 and NCT02833792) were using intravenously injected MSCs cells: the first one autologous adipose-derived MSCs from a patient's liposuction and the second one ischemia-tolerant allogenic human bone-marrow-derived MSCs.

In conclusion, even if MSCs, as well as NSCs and autologous hematopoietic stem cells, can lead to a tumorous formation, MSCs are promising to enhance the cognitive function and the life quality but cannot fully restore the neuronal loss in AD.

MULTIPLE SCLEROSIS

In 2003, in an article on Nature, an experiment, in which cultures of syngeneic adult neural stem cell were injected into a mouse with an experimental autoimmune encephalomyelitis (EAE) either intravenously or intracerebroventricularly, was discussed. The result was that many donor cells reached the demyelinating areas differentiating into mature brain cells. Moreover, the number of oligodendrocyte progenitors raised remyelinating axons, while astrogliosis, demyelination and axonal loss decreased. Finally, the injection of adult neural precursors led to remyelination and functional recovery in the model (3).

In 2012, in the Cell Transplant, another experiment was described. In this case, the implantation of neural stem cells (NSCs) intraventricularly was performed in an acute experimental autoimmune encephalomyelitis (EAE) animal. The therapeutic cellular mechanism was associated to immune regulation and, in addition, NSCs became oligodendrocyte precursor cells (OPCs) by a provisory overexpression of Olig2, which led to a functional recovery by contributing to the remyelination. After the injection, NSCs and Olig2-NSCs entered the active lesions in the spinal cord and then many Olig2-NSCs differentiated into OPCs, instead the NSCs are undifferentiated. However, both types of cells led to a reduction of the acute clinical signs and of the relapses. In general, this demonstrates that this treatment may be very useful in the relapsing-remitting phases of MS and in the prevention of chronic progressive disease (4).

SPINAL CORD INJURY

In 2009 in Neuroscience, a study was published by Dong H Hwang, et al (6) about the transplantation of Olig2-NSCs to enhance locomotor recovery and myelination in a rat contusive spinal cord injury model.

Since a spinal cord contusion is followed by a retarded loss of oligodendrocytes and therefore a chronic progressive demyelination, an implantation of oligodendrocytes seems to be the best solution for spinal cord repair. Exactly, in this experiment, a HB1.F3 (F3) immortalized human NSC line was created using a retroviral vector encoding Olig2. The overexpression of this lineage activates NKX2.2 leading to a NSCs differentiation into oligodendrocytes in vitro as well to higher proliferative activity of the cells. Moreover, F3. Olig2 NSCs penetrate the white matter differentiating into oligodendrocytes, whereas F3 NSCs remain in the gray matter or around the lesion cavities. Therefore, a transplantation of F3. Olig2 NSCs increases the volume of spared white matter and the thickness of myelin around the axons in that area. Finally, in the experiment, F3. Olig2 grafts enhance the quality of hindlimbs locomotion and, in general, the functional outcomes after a spinal cord trauma.

In 2012 in Neurotherapeutics, an article by Jian-Guo Hu, et al (5) was published regarding the effects of Olig2-NCSs and myelin basic protein-activated T (MBP-T) cells to help in the recovery after a spinal cord injury. In this experiment, first MBP-T cells were passively immunized, then Olig2-NSCs were infected with a lentivirus carrying the enhanced green fluorescent protein (GFP) reporter gene to create Olig2-GFP-NSCs. These cells were later transplanted into the damaged area to allow the differentiation into OLs. Even the MBP-T cells were also transferred in the same area and penetrated the injured spinal cord. Then they produced neurotrophic factors promoting the differentiation of resident microglia and/or blood monocytes into anti-inflammatory macrophage phenotype. In general, it was observed that, in association with MBP-T cell and Olig2-GFP-NSC, the number of OL-remyelinated axons raised, the spinal cord lesion volume was reduced, and the spared myelin and recovery were improved. This study suggests that MBP-T cells together with NSC transplantation seems to promote the recovery after traumatic spinal cord injury.

ARACHNOIDITIS AND OTHER ASSOCIATED DISEASES

Until now, a stem cell therapy in arachnoiditis has not yet been studied. However, in medical literature, we can find articles about this disease as an adverse effect of stem cell therapy or as a complication of another disease as it is specified below. An explanation of this medical condition and its associations with other diseases such as type 1 ACM, syringomyelia and Ehlers-Danlos-syndromes will also follow.

As described by Ajay A Madhavan, et al (17.) in the Neuroradiology Journal in 2020, an intrathecal stem cell transplantation caused a case of lymphocytic infiltrate with arachnoiditis. Exactly, in Moscow (Russia), a 74-year-old patient male underwent an intrathecal transplantation of stem cells for weakness and fatigue. After this procedure, he was presenting progressive weakness in the extremities and urinary incontinence. In the MRI of the thoracic and lumbar spine, it was found out that the cauda equina nerve roots were enlarged, and a mass was in the thoracolumbar thecal sac. A surgical biopsy showed a polyclonal lymphatic infiltrate and, unfortunately, medical treatment and radiation did not improve the symptoms. However, it must be said that nervous system neoplasms can represent the worse scenario after such procedures.

A severe intraventricular hemorrhaging (IVH) in premature infants can also lead to an obliterative arachnoiditis. However, it is important to mention that the following posthemorrhagic hydrocephalus (PHH) is life-threatening causing a high percentage of mortality. If the infants do not die, they can have many neurological complications including seizures, cerebral palsy, or developmental retardation. As the PHH can be explained by the inflammatory response in the subarachnoid spaces, in the same way, this can clearly be the reason for the obliterative arachnoiditis, which does not allow the resorption of the cerebrospinal fluid (CSF) leading secondly to a PHH. Transplanted MSCs in an IVH model of newborn rats can downregulate the inflammatory process reducing the effect of a PHH progression and the brain damages after IVH and PHH. In general, the study shows a good grade of neuroprotection in such animal models (Ahn SY, et al, 2014). Another study was focused on the perfect timing for this therapy. The implantation of the human umbilical cord blood (UCB) - derived MSCs - was done intraventricularly at the day 6 and 11. The rats were monitored using MRIs and behavioral tests, at the day 32 tissue samples were taken showing a reduction of PHH and of the brain injuries. However, the best grade of neuroprotection was demonstrated between 2 and 7 days after the MSCs transplantation (19). In a phase I dose-escalation clinical trial in 9 premature infants, 3 of them received a low dose of MSCs (5×10^6 cells/kg), and 6 a high dose (1×10^7 cells/kg). The implantation was well tolerated, and no infants died, but patients that underwent a shunt operation had high level of IL6 in the CSF before the procedure, when compared to the other ones without it. The result was that this phase I was safe and a large phase II study is possible (20).

In general, adhesive arachnoiditis, also known as spinal arachnoiditis, is a rare inflammatory disease of the arachnoid membrane and often found in correlation with Tarlov cysts (TC) (49). The etiology is still unclear, but it is associated to spinal trauma, hemorrhagic events, spinal surgeries, or iatrogenic maneuvers such as myelograms with oil-based radiographic contrast agents. The gold standard for the diagnosis is the patient's symptomatology together with an MRI. However, since arachnoiditis can mimic many other diseases including spinal cord tumors, arachnoiditis ossificans, syringomyelia, sciatica pain and a cauda equina syndrome (36), it is often misdiagnosed and often not recognized as disease by many doctors. Nowadays, there is no treatment for this disease and research using stem cells therapy should be taken in consideration. Arachnoiditis can be associated to Arnold Chiari I malformation (type I ACM). For instance, reports describe a Chiari I after a distal tuberculous arachnoiditis in the lumbar spine. Another association is between arachnoidids and syringomyelia. However, the pathophysiology beyond these connections is still unclear (37-40).

Exactly, unlikely Chiari from types 2 to 4, Chiari I malformation should be considered a syndrome and therefore called Chiari syndrome (41). A case of Arnold Chiari syndrome was documented in a 53-year-old woman with papilledema, who has already been treated oncologically and surgically due to right breast tumor 4 years earlier. In a brain MRI, metastasis was excluded, and a Chiari malformation diagnosed. At this point, it is assumed that the papilledema was an expression of the intracranial hypertension mainly caused by the Chiari malformation (42).

Another case of idiopathic intracranial hypertension and Chiari deformity was described in an obese pregnant woman. In this case, the cerebral CT scan was normal. After acetazolamide use, she had an alteration of her neurologic state and ocular motility. MRI was performed and showed a type I ACM. First, a decompression of the cerebrospinal fluid (CSF) by superior way and then a neurosurgical surgery for the Chiari malformation were conducted leading to a total patient's recuperation. A lumbar punction could be fatal. Maybe, in this case, the idiopathic intracranial hypertension was responsible for a decompensation of the ACM (43).

Arachnoid granulation (AGs) was found in idiopathic intracranial hypertension (IIH). In a retrospective study, 79 patients with a diagnosis of IIH were compared with 63 patients with multiple sclerosis. MRI of the brain, older than 18 years old and females were the inclusion criteria. Finally, the percentage of patients with AGs was higher in the group with IIH. In these patients, the relationship between AGs and IIH can be explained as a compensatory mechanism in the arachnoid because of the IIH (44).

After a subarachnoid hemorrhage, a case of adhesive arachnoiditis and dorsal syringomyelia was also described (45). In another article, a 66-year-old patient with a primary Sjögren syndrome had a syringomyelia after two subarachnoid hemorrhages (SAHs). Exactly, three years after the last SAH, she started to have gait disturbance and pain in the abdomen and foot. In the MRI, a syringomyelia from T2 to T11 and multiple arachnoid cysts in the spinal cord were described. Surgically, a microlysis of the adhesions with a following CSF restoration was performed. Afterward, the

patient could walk again, but the abdominal paresthesia did not improve. An MRI showed a reduced size of the syrinxes. This demonstrates that a syringomyelia and arachnoid cysts can be a late complication of SAH and that surgical treatment is the best choice to improve this condition (46).

To better understand the possible connections between the three diseases, namely arachnoiditis, type 1 ACM and syringomyelia, this last medical condition will be described in detail below.

S*yringomyelia* is a progressive and chronic condition. The syrinx is a fluid-filled cavity in the spinal cord, or a focal dilatation of the central canal called hydromyelia. There is a congenital form, or more exactly two types, caused by abnormality of primary neurulation, and an acquired one. In the first form, we can distinguish an embryogenic type and a fetal one. While, in the embryogenic type, there is an abnormal dilatation of the spinal cord canal with an absence of mesenchymal tissue between the spinal cord and the ectoderm; the fetal one does not show an affection of the mesenchymal tissue, therefore the vertebral column is intact. Instead, the acquired form is characterized by a disturbance of the normal cerebrospinal fluid dynamics. The etiologies of the congenital form are neural tube defects and *Chiari-I malformation*. Chiari-I malformation is caused by a downward herniation of the cerebellar tonsils, which blocks the CSF flow during the cardiac cycle and Valsalva maneuvers. In the acquired form, causes can be secondary to hydrocephalus; infection such as a meningitis; inflammation including transverse myelitis, sarcoidosis, and multiple sclerosis; trauma such as surgery and arachnoid scarring in *adhesive arachnoiditis*; extramedullary lesions such as arachnoid cysts and tumors; intramedullary tumors such as hemangioblastomas and ependymomas; and spinal canal stenosis especially in the cervical area. Patients with syringomyelia can be asymptomatic or have pain accompanied by weakness and stiffness in back, extremities, and shoulders. They can experience a reduction of sensation for extreme hot or cold in their hands, and of temperature sensation in the back and arms. In the end-stage, an autonomic bladder and a bowel dysfunction can appear. In the congenital form with a neural tube defect, the patients have neurological problems in the legs, bladder and bowel dysfunction and pain. Scoliosis is often described, especially in patients with a terminal syrinx, but the ones having an extension of the syringomyelia in the cervical area cord also have sensory symptoms and hand weakness. The diagnosis is done through an MRI scan, especially an electrocardiographically gated flow-sensitive technique, such as four-dimensional (4D) phase contrast (PC) MRI. In asymptomatic syringomyelia, the therapy is "wait and watch", instead the symptomatic syringomyelia is treated in a nonsurgical way with medication. In neural tube defects, a shunt revision is often associated with an improvement of the symptoms, however, in case of unsuccess, the untethering of the cord is considered beneficial. On follow-up MRI, after a successful untethering, a syrinx can appear larger than before (48). In other cases, for example like Chiari-I malformation, it is important a surgical treatment with a craniocervical decompression and an augmentation duraplasty. In arachnoid scarring, such as in the case of adhesive arachnoiditis, localized bands of fibrosis can be sectioned performing an adhesiolysis, but in the case of a widespread arachnoiditis with infiltration of dura, arachnoid, and pia matter sometimes it is impossible, and the only solution is to direct drainage of the syrinx. Postoperative complications can be infections, hematomas, and scar formation close to the spinal cord or implanted shunts with their possible obstruction, and wound leakage of CSF. The prognosis is not good, since it is a progressive chronic disease with remissions and exacerbations, that often require surgical intervention to avoid a loss of functions (47).

And finally, there is also an association between arachnoiditis and Ehlers-Danlos syndromes (EDS). To describe briefly what EDS are, we can say that these conditions are a group of connective tissue disorders. Patients suffering with these syndromes have normally skin extensibility, joint hypermobility, and tissue fragility. This leads to neurological problems, such as weakness of the ligaments of the craniocervical junction and spine, and of the epineurium and perineurium close to the peripheral nerves, and early disc degeneration. A prevalence of IIP and TCs were reported but unfortunately there is not real epidemiological evidence. Even Chiari Malformation Type I can be a comorbid condition in such patients (51).

In conclusion, we can see that an arachnoiditis is often associated with congenital or acquired diseases, which can cause a block of the normal CSF flow dynamics and therefore an inflammation of the arachnoids. It would be very useful to focus on the study of this disease and its associations since this could open the horizon to cure many neurological problems and help to improve patient's life.

CONCLUSION

In conclusion, we can say that stem cells are very important for many reasons. They can be useful to study of the human development and the regenerative potential, as well as the etiopathogenetic mechanisms and pathophysiology of various diseases, and, additionally, they are used to develop biological models for testing new pharmacological agents. Finally, they can replace damaged tissue and regenerate organs. Since many clinical studies have been performed and showed good results in terms of therapeutic strategies in cell-based medicine, an increase in ethical issues and dangers has also been observed. However, there are many promising studies, which lead to hoping for a brighter future with regards to regenerative medicine. At a biological level, it is important to mention miRNAs in the stem cells cycle regulation considering that these are responsible for the self-renewal and pluripotency in ESCs and in the regulation of CSCs.

Moreover, some miRNAs are associated with a good prognosis in cancer patients. Therefore, the study of CSC-related miRNAs is essential for clinical purposes.

Stem cell therapy in neurodegenerative diseases such as Alzheimer's and Parkinson's disease has been demonstrated to be very useful in reducing the symptoms, but further studies and clinical trials to block the progression of these diseases are still needed. Adhesive arachnoiditis as well as other types of arachnoiditis and their associations with other

congenital or acquired diseases need to be understood better and experiments with stem cells should be started soon.

BIBLIOGRAPHY

1. George Kolios and Yuben Moodley, Introduction to stem cells and regenerative medicine, Respiration 2013; 85:3-10; Epub 2012 Dec 13.
2. Michelle M J Mens, Mohsen Ghanbari. Cell Cycle Regulation of Stem Cells by MicroRNAs. Stem Cell Rev Rep, 2018 June; 309-322.
3. Stefano Pluchino, Angelo Quattrini, Elena Brambilla, Angela Gritti, Giuliana Salani, Giorgia Dina, Rossella Galli, Ubaldo Del Carro, Stefano Amadio, Alessandra Bergami, Roberto Furlan, Giancarlo Comi, Angelo L Vescovi, Gianvito Martino. Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. Nature 2003 Apr 17; 422 (6933): 688-94.
4. Falak Sher, Sandra Amor, Wouter Gerritsen, David Baker, Samuel L Jackson, Erik Boddeke, Sjef Copray. Intraventricularly injected Olig2-NSCs attenuate established relapsing-remitting EAE in mice. Cell Transplant 2012; 21(9): 1883-97. Epub 2012 March 28th.
5. Jian-Guo Hu, Lin Shen, Rui Wang, Qi-Yi Wang, Chen Zhang, Jin Xi, Shan-Feng Ma, Jian-Sheng Zhou, He-Zuo Lü. Effects of Olig2-overexpressing neural stem cells and myelin basic protein-activated T cells on recovery from spinal cord injury. Neurotherapeutics 2012 April; 9 (2): 422-45.
6. Dong H Hwang, Byung G Kim, Eun J Kim, Seung I Lee, In S Joo, Haeyoung Suh-Kim, Seongyang Sohn, Seung U Kim. Transplantation of human neural stem cells transduced with Olig2 transcription factor improves locomotor recovery and enhances myelination in the white matter of rat spinal cord following contusive injury; BMC Neuroscience 2009 Sep 22; 10:117.
7. Lucie Bacakova, Jana Zarubova, Martine Travnickova, Jana Musilkova, Julia Pajorova, Petr Slepicka, Nikola Slepickova Kasalkova, Vaclav Svorcik, Zdenka Kolska, Hooman Motajemi, Martin Molitor. Stem cells: their source, potency and use in regenerative therapies with focus on adipose-derived stem cells - a review. Biotechnol Adv, Jul-Aug 2018; 36 (4): 1111-1126. Epub 2018 Mar 18.
8. Farshid Huilak, Bradley T. Estes, Brian O. Diekman, Franklin T. Moutos, Jeffrey M. Gimble. 2010 Nicolas Andry Award: Multipotent adult stem cells from adipose tissue for musculoskeletal tissue engineering. Clin Orthop Relat Res 2010 Sep; 468 (9): 2530-40. Epub 2010 Jul 13.
9. Yue Xu, Wan-Xia Zhang, Li-Na Wang, Yue-Qing Ming, Yu-Lin Li, Guo-Xin Ni. Stem cell therapies in tendon-bone healing. World J Stem Cells 2021 Jul 26; 13(7): 753-775.
10. Sunhee Jang, Kijun Lee and Ji Hyeon Ju. Recent Updates of Diagnosis, Pathophysiology, and Treatment on Osteoarthritis of the Knee. Int J Mol Sci 2021 Mar 5; 22 (5):2619.
11. Ai-Tong Wang, Ying Feng, Hong-Hong Jia, Meng Zhao, Hao Yu. Application of mesenchymal stem cell therapy for the treatment of osteoarthritis of the knee: A concise review. World J Stem Cells 2019 Apr 26; 11(4): 222-235.
12. Abderrahim Naji, Masamitzu Eitoku, Benoit Favier, Frédéric Deschaseaux, Nathalie Rouas- Freiss, Narufumi Suganuma; Biological functions of mesenchymal stem cells and clinical implications; Cell Mol Life Sci 2019 Sep, 76 (17): 3323-3348. Epub 2019 May 4.
13. Wojciech Marlicz, Igor Loniewski, Karolina Skonieczna-Zydecka. Stem and Progenitor Cells in the Pathogenesis and Treatment of Digestive Diseases. Adv Exp Med Biol 2019; 1201: 125-157.
14. Ben Mead, Martin Berry, Ann Logan, Robert A H Scott, Wendy Leadbeater, Ben A Scheven; Stem cell treatment of degenerative eye disease; Stem Cell Res 2015 May 14, Epub 2015 Feb 24
15. Ting-Hsing Chao, I-Chih Chen, Shi-Ya Tseng, Yi-Heng Li. Pluripotent Stem Cell Therapy in Ischemic Cardiovascular Disease. Acta Cardiol Sin. 2014 Sep; 30 (5): 365-74.
16. Thomas Duncan, Michael Valenzuela. Alzheimer's disease, dementia and stem cell therapy; Stem Cell Res. Ther. 2017 May 12; 8 (1): 111.
17. Ajay A Madhavan, Dan Summerfield, Christopher H Hunt, Dong K Kim, Karl N Krecke, Aditya Raghunathan, John C Benson. Polyclonal lymphocytic infiltrate with arachnoiditis resulting from intrathecal stem cell transplantation. Neuroradiol J 2020 Apr; 33 (2): 174-178. Epub 2020 Feb 3.
18. So Yoon Ahn, Yun Sil Chang and Won Soon Park; Mesenchymal stem cells transplantation for neuroprotection in preterm infants with severe intraventricular hemorrhage; Korean J Pediatr 2014 Jun; 57 (6): 251-6. Epub 2014 Jun 30.
19. Won Soon Park, Se In Sung, So Yoon Ahn, Dong Kyung Sung, Geun Ho Im, Hye Soo Yoo, Soo Jin Choi, Yun Sil Chang. Optimal Timing of Mesenchymal Stem Cell Therapy for Neonatal Intraventricular Hemorrhage. Cell Transplant 2016; 25(6): 1131-44. Epub 2015 Oct 5.
20. So Yoon Ahn, Yun Sil Chang, Se In Sun, Won Soon Park. Mesenchymal Stem Cells for Severe Intraventricular Hemorrhage in Preterm Infants: Phase I Dose-Escalation Clinical Trial. Stem Cells Transl Med 2018 Dec: 7 (12): 847-856. Epub 2018 Aug 21.
21. Ruth B Schneider, Julia Iourinets, Irene H Richard. Parkinson's disease psychosis: presentation, diagnosis, and management. Neurodegener Dis Manag 2017 Dec: 7 (6): 365-376. Epub 2017 Nov. 21.
22. Yossef S Levy, Merav Stroomza, Eldad Melamed, Daniel Offen. Embryonic and adult stem cells as a source for cell therapy in Parkinson's disease. J Mol Neuroscience 2004; 24 (3): 353-86.
23. Seung U Kim. Human neural stem cells genetically modified for brain repair in neurological disorders. Neuropathology 2004 Sep; 24 (3): 159-71.
24. Johannes Winkler, Jürgen Hescheler, Agios Sachinidis. Embryonic stem cells for basic research and potential clinical applications in cardiology. Biochim Biophys

Acta 2005 May 30; 1740 (2): 240-8. Epub 2004 Dec 9.
25. G Bartsch Jr, D Frimberger. Embryonic and adult stem cells for tissue engineering in urology. Urologe A 2004 Oct; 43 (10): 1229-36.
26. Yogita Sharma, K Shobha, Mata Sundeep, Venkata Bharatkumar Pinnelli, Shagufta Parveen, Anandh Dhanushkodi. Neural Basis of Dental Pulp Stem Cells and its Potential Application in Parkinson's Disease. CNS Neurol Disord Drug Targets 2022; 21 (1): 62-76.
27. Anna Nelke, Silvia Garcia-Lopez, Alberto Martinez-Serrano, Marta P Pereira. Multifactoriality of Parkinson's Disease as Explored Through Human Neural Stem Cells and Their Transplantation in Middle-Aged Parkinsonian Mice; Front Pharmacol 2022 Jan 19; 12: 773925. eCollection 2021.
28. Monika Vinish, Sudesh Prabhakar, Madhu Khullar, Indu Verma, Akshay Anand. Genetic screening reveals high frequency of PARK2 mutations and reduced Parkin expression conferring risk for Parkinsonism in North West India. J Neurol Neurosurg Psychiatry 2010 Feb; 81 (2): 166-70. Epub 2009 Sep 3.
29. Ekaterina Novosadova, Ksenia Anufrieva, Elizaveta Kazantseva, Elena Arsenyeva, Viya Fedoseyeva, Ekaterina Stepanenko, Daniil Poberezhniy, et al. Transcriptome datasets of neural progenitors and neurons differentiated from induced pluripotent stem cells of healthy donors and Parkinson's disease patients with mutations in the PARK2 gene; Data Brief 2022 Feb 16; 41: 107958. eCollection 2022 Apr.
30. Zhengqin Sun, Ping Gu, Hongjun Xu, Wei Zhao, Yongjie Zhou, Luyang Zhou, Zhongxia Zhang, Wenting Wang, Rui Han, Xiqing Chai, Shengjun An. Human Umbilical Cord Mesenchymal Stem Cells Improve Locomotor Function in Parkinson's Disease Mouse Model Through Regulating Intestinal Microorganisms. Front Cell Dev Biol 2022 Jan 20; 9: 808905. eCollection 2021.
31. Javier Jarazo, Kyriaki Barmpa, Jennifer Modamio, Claudia Saraiva, Sonia Sabate-Soler, Isabel Rosety, Anne Griesbeck, Florian Skwirblies, Gaia Zaffaroni, et al. Parkinson's Disease Phenotypes in Patient Neuronal Cultures and Brain Organoids Improved by 2-Hydroxypropyl-β-Cyclodextrin Treatment. 28. Mov Disord 2022 Jan; 37 (1): 80-94. Epub 2021 Oct 12.
32. Armin Blesch, Mark H Tuszynski. Gene therapy and cell transplantation for Alzheimer's disease and spinal cord injury. Yonsei Med J 2004 Jun 30; 45 Suppl: 28-31.
33. Nikolaos Karvelas, Samuel Bennett, Georgios Politis, Nikolaos-Iasonas Kouris, Christo Kole. Advances in stem cell therapy in Alzheimer's disease: a comprehensive clinical trial review. Stem Cell Investig 2022 Feb 21; 9: 2. eCollection 2022.
34. Jingqiong Hu, Xiaochuan Wang. Alzheimer's Disease: From Pathogenesis to Mesenchymal Stem Cell Therapy - Bridging the Missing Link. Front Cell Neuroscience 2022 Feb 7; 15: 811852. eCollection 2021.
35. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126(4):663–676.
36. Michael H Wright, Leann C Denney. A comprehensive review of spinal arachnoiditis. Orthop Nurs May-Jun 2003; 22(3):215-9; quiz 220-1.
37. Andreas K Demetriades. Arachnoiditis and Chiari I malformation. Acta Neurochir (Wien) 2021 Jan;163(1):227-228. Epub 2020 Sep 18.
38. Heidary M, Respondedk M, Klekamp J. Histological and intraoperative evaluations of the arachnoid in patients with Chiari I malformation. Acta Neurochir (Wien). 2021 Jan; 163 (1): 219-225.
39. Holly LT, Batzdorf U (2019) Chiari malformation and syringomyelia. J Neurosurg Spine 31(5):619–628.
40. Klekamp J, Iaconetta G, Batzdorf U, Samii M (2002) Syringomyelia associated with foramen magnum arachnoiditis. J Neurosurg 97(3 Suppl): 317–322.
41. Radek Fric, Per Kristian Eide. Chiari type 1-a malformation or a syndrome? A critical review. Acta Neurochir (Wien) 2020 Jul;162(7):1513-1525; Epub 2019 Oct 28.
42. Barbara Zatorska, Ewa Herba, Dorota Pojda-Wilczek, Wojciek Jedrzejewski, Stefan M Pojda. The intracranial hypertension in the course of Arnold-Chiari malformation. Klin Oczna 2004;106(4-5):657-60.
43. P Demols, C Van Nechel. Association of idiopathic intracranial hypertension-Arnold-Chiari deformity: danger!Bull Soc Belge Ophtalmol 1998;268:153-8.
44. Gaurav Vishwasrao Watane, Bhumi Patel, Derek Brown, M Reza Taheri. The Significance of Arachnoid Granulation in Patients With Idiopathic Intracranial Hypertension. J Comput Assist Tomogr Mar/Apr 2018;42(2):282-285
45. Rafael Galiano, Arantxa, Navarre-Gimeno, Vicente Miranda-Gonzalbo, Miguel Garcia-Escrig, Iratxe Jimenez, Luis Aznar. Adhesive arachnoiditis and dorsal syringomyelia secondary to subarachnoid haemorrhage. Rev Neurol 2013 Jun 16;56(12):639-40.
46. Shunsuke Ishizaka, Kentaro Hayashi, Munehiro Otsuka, Shuji Fukuda, Keishi Tsunoda, Ryujiro Ushijima, Naoki Kitagawa, Kazuhiko Suyama, Izumi Nagata. Syringomyelia and arachnoid cysts associated with spinal arachnoiditis following subarachnoid hemorrhage. Neurol Med Chir (Tokyo) 2012;52(9): 686-90.
47. W. Peter Vandertop, Syringomyelia, Neuropediatrics 2014 Feb;45(1):3-9. Epub 2013 Nov 22.
48. Vandertop WP. Progression of terminal syrinx in occult spina bifida. Childs Nerv Syst 2003; 19 (5-6) 267, author reply 268.
49. Prof. Jan-Peter Warnke MD PhD, Presentation "Tarlov cyst and Pain". Crowdcast 2021 March 17, Paracelsus-Klinik Zwickau.
50. Soo Jung Cho, et al. Drosha-Dependent miRNA and AIM2 Inflammasome Activation in Idiopathic Pulmonary Fibrosis. Int. J. Mol. Sci. 2020, 21 (5), 1668.
51. Fraser C. Henderson Sr., Claudiu Austin, Edward Benzel, Paolo Bolognese, Richard Ellenbogen, Clair A Francomano, et al. Neurological and spinal manifestations of the Ehlers-Danlos syndromes. American Journal of Medical Genetics Part C: Seminars in Medical Genetics, Volume 175, Issue 1/p. 195-211, Epub 2017 February 21.