Human Cell Models of Disease

Subjects: Biochemistry & Molecular Biology

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Neurological disorders, including neurodegenerative diseases, are collectively a major cause of death and disability worldwide. Altered mitochondrial function has been implicated in nearly all of these diseases. A variety of cultured cell models have been used to study these diseases including lymphocyte cells immortalized with Epstein Barr Virus. These cell models have been useful in deciphering the role of the mitochondria in these disorders.

lymphoblastoid cell lines | mitochondria | neurodegenerative disease | neurological disorder | cultured human cells

1. Introduction

The mitochondria, tiny organelles present in all but a few human cell types, are best known as the energy powerhouses of the cell, responsible for producing more than 90% of the cell's energy in the form of ATP. In addition to producing ATP, the mitochondria participate in other critical central metabolic pathways, such as apoptosis, generation of reactive oxygen species (ROS), division and proliferation, lipid biosynthesis and degradation as well as signalling networks, including calcium, hormone and immune signalling pathways. Given these essential and diverse roles, it is not surprising that mitochondrial dysregulation or dysfunction is linked to many diseases, including neurological and neurodegenerative disorders. Investigating mitochondrial function/dysfunction is key to understanding the pathogenesis of these diseases and has also been shown to be useful in both diagnosis and prognosis.

Understanding of mitochondrial roles in disease has been greatly facilitated by the use of simple eukaryotic and animal models, including yeast, slime moulds, nematodes and flies [1][2][3][4][5][6][7][8]. These genetic models are based on gene mutations of genes associated with relatively rare familial neurodegenerative disorders and may not faithfully recapitulate what is happening in the more common sporadic cases of neurological disorders. This is supported by a number of therapeutic agents that only show benefit in familial disease models and not in sporadic disease cases [9].

In addition to these models, human cell lines, including primary cell lines, have provided invaluable insights into cellular disease mechanisms. Neurodegenerative and neurological disorders are characterised by death or dysfunction of neurons in the brain, but the underlying disease mechanism may be more systemic, also occurring in other cell types and tissues. This is supported by studies which show that peripheral tissues, such as blood, recapitulate the transcriptional changes that occur in the brain of patients with neurodegenerative disease [10][11][12]

[13]. The exact mechanism of the neuronal cell death is unknown, but in addition to the diverse collection of clinically described diseases arising from genetic forms of mitochondrial disease, mitochondrial dysfunction has been clearly implicated in many, including Alzheimer's (AD) [14], Parkinson's (PD) [15] and Huntington's (HD) [16] disease as well as Fragile-X-associated Tremor and Ataxia syndrome (FXTAS) [17]. Mitochondrial dysfunction could be occurring systemically throughout the body in these disorders, but the effects would be more obvious in energy-demanding organs, such as in muscles and the brain. Neurons consume large amounts of energy and are postmitotic long-lived cells, which limits their regenerative capacity so that over time, mitochondrial dysfunction would lead to increased ROS production, increased mtDNA damage and worsening of mitochondrial function. This process of accumulated damage occurs naturally in ageing and is suggested to provide the link between neurodegenerative diseases and the biggest risk factor, ageing. Altered mitochondrial function in many neurodegenerative diseases is likely to be systemic, occurring in most tissues of the body. Indeed, the dysregulated expression of genes involved in metabolism and mitochondrial function has been identified in peripheral cells, such as blood and skin, of neurodegenerative disease patients [10][11].

If the mitochondrial dysfunction is systemic, then other, more accessible tissue may be used to characterise the dysfunction, use it as biomarkers of the disease and also to test the level or severity of the dysfunction in relation to clinical parameters. The most accessible tissue of the human body is blood. Compared to neurons, peripheral blood lymphocytes are short lived, rapidly turned over and, when activated, they become proliferative. These differences need to be taken into account when interpreting data from these cell types.

2. Types of Human Cellular Disease Models

There are many commercial cell lines available for use in the laboratory, and these are commonly obtained from cancerous tissue or are transformed with a tumour-inducing virus and have chromosomal abnormalities or mutations which enable them to continue proliferating in cell culture and are termed immortalised. The most commonly used and oldest cell line is the HeLa cell line, which was isolated from cervical cancer tissue from a patient called Henrietta Lacks in 1951 [18]. This cell line has contributed to many of the major advances in cancer biology and fundamental microbiology. It has also been used to expand our knowledge of neurodegenerative disease, such as characterising mitochondrial defects after expression of the mutant huntingtin (Huntington's disease protein) [19] and also to study processes associated with neurodegeneration, such as autophagic clearance [20]. Whilst very useful and popular—a keyword search for HeLa cells in the last decade identifies more than 10,000 publications—this cell line has its limitations. It has been shown by several research groups that HeLa cell lines have diversified over the years and HeLa cells from different research groups are significantly different from one another, with differences in their genomes, mRNA expression levels and copy number variations (the number of repeats of a given gene) [21]. This raises the question of the reproducibility and generalisability, even to other HeLa cultures, of findings made in such a model.

Another commonly used cell line is HEK293 and its derivatives, frequently used for its ease of culturing and transfection. Due to these attributes, HEK293 cells have been used to express mutant proteins associated with neurodegenerative disease, such as α-synuclein, LRRK2 and Tau in Parkinson's and Alzheimer's disease [22][23][24].

The HEK293 cell line was established from primary embryonic human kidney cells, transformed with sheared human adenovirus type 5 DNA [25]. The adenovirus DNA was integrated into human chromosome 19, and the cell line displays several chromosomal abnormalities, including extra copies of the X, 17 and 22 chromosomes, with the exact number of chromosomes differing between laboratory isolates [26][27].

Cell lines such as the catecholaminergic cell lines SH-SY5Y and PC12 are commonly used for studying aspects of neurological disorders, especially Parkinson's disease, which affects the dopaminergic neurons. These cell lines have the machinery necessary to synthesise, release and store catecholamines, particularly dopamine, and can be differentiated into post-mitotic neuronal or neuron-like cells. SH–SY5Y cells were generated from a bone marrow biopsy of a metastatic neuroblastoma [28] and can be differentiated into a mature neuronal phenotype by several methods with the most common method involving exposure to retinoic acid [29]. SH–SY5Y cells have been used to understand PD disease processes and α-synuclein's role in altered PD mechanisms (reviewed in [30]). The PC12 cell line was derived from a pheochromocytoma of the rat adrenal medulla. These cells are embryonic in origin but can differentiate into sympathetic ganglion neurons after culturing with nerve-growth factor [31]. They display many features of neuronal cells, they can synthesis and store dopamine, they express synapsin I protein, a marker of synaptic communication, and contain Toll-like receptors (TLR4), important in neuroinflammation [32]. These neuron-like differentiated cells have been used to model neurodegenerative diseases, including Alzheimer's disease [33] and Amyotrophic Lateral Sclerosis [34]. These cell lines, whilst very useful, have some limitations. Like other cancerous cell lines, these cell lines also display a number of genetic aberrations [35]. Differences in growth, culturing and differentiation conditions can result in changes to the metabolome, proliferation and differentiation capacity [29][32] and these need to be taken into consideration when analysing results, especially across different laboratories, and could hinder use in high-throughput procedures.

In contrast, Lund human mesencephalic (LUHMES) cells are not as susceptible to changes in culturing conditions and can also be induced to differentiate into neuronal cells. These cells are derived from human embryonic mesencephalon and were immortalised via introduction of a tetracycline-responsive v-myc gene [36]. The cells can differentiate into mature dopaminergic neuron-like cells by culturing them with tetracycline, cAMP and glial cell-derived neurotrophic factor (GDNF) [36]. Unlike the neuron-like cells discussed above, LUHME cells display electrical activities [37].

Whilst these commercial cell lines are extremely useful for studying gene function, the production of proteins and so on, they do not fully recapitulate what is happening in vivo and hence, primary cell lines and derivatives thereof may be more useful for modelling complex neurological human diseases. These models provide a tool for analysing cells taken directly from patients that retain genetic information, including mutations and epigenetic markers, which can then be compared to similar cell lines from healthy controls. Primary cell lines can be generated from a number of tissues, but the two most accessible human tissues are skin and blood.

Skin tissue can be used to isolate and grow primary fibroblast cell lines, which can be cultured for up to *ca.* 50 cell doublings [38]. The replicative ability of fibroblasts in culture is affected by several factors, including the location of the body that the skin was isolated from [39], health [40], and in some reports, the age of the patient, with an inverse

relationship between age and the proliferative ability of fibroblasts [41]. The number of culture passages they have passed through since isolation and the density of the culture from which they were drawn also affect the physiological state and replicative ability of fibroblasts [42]. Therefore, care must be taken when using fibroblast cells from patients to account for these differences.

By far the most accessible tissue of humans is blood, and samples can be taken on multiple occasions from the same participant. Peripheral Blood Mononuclear Cells (PBMCs) are routinely isolated from blood, and contain a mixture of lymphocytes (T cells, B cells, and NK cells) (70–90%), monocytes (10–20%), and dendritic cells (1–2%) [43]. The relative proportions of each cell type vary between individuals and are influenced by inflammation and disease-related processes. These cells do not survive outside the body and can only survive in laboratory conditions for about 5 days. The cells are not actively proliferating and are metabolically quiescent, so differences between patient and control groups may be obscured [44].

A limitation with all primary cell lines is that they do not grow indefinitely and, therefore, repeat sampling is often required, something which is not always possible and can result in participants being lost to the study. Once these cells are taken from the body, they begin a process of cellular ageing, culminating in senescence at rates that differ for different cell types, different individuals, and potentially even different participant groups (e.g., disease vs. control). Quite apart from, or even because of, the differences in their ex vivo and in vivo environments, ex vivo primary cell cultures and their in vivo counterparts cannot be considered equivalent. For example, from the few in vivo measurements that have been made, the rate of proliferation of fibroblasts in culture far exceeds their proliferation and turnover rates in vivo [38]. This implies corresponding differences in the in vivo and ex vivo metabolic and physiological states of the cells. So long as this is kept in mind, the study of primary cell lines can and has made many invaluable contributions to our understanding of mitochondria and neurodegenerative disorders. These include the use of fibroblast cell lines from PD patients to understand the function of a key PD-associated protein, PINK1 [45], and the use of PBMCs to detect altered gene expression of proteins to use as biomarkers of Alzheimer's disease [46][47].

Multipotent stem cells, namely neuronal precursor cells (NPC) and oligodendrocyte precursor cells (OPCs), have been used to study neurodegenerative disorders, such as OPCs in ALS [48] and NPCs in Parkinson's disease [49]. These precursor cells are extracted from the spinal cord, usually from embryos, and show some promise in therapies involving transplantation. With the development of induced pluripotent stem cells iPSCs by Takahashi and Yamanaka in 2006 [50], their use in modelling neurodegenerative disease has become widespread, and biobanked iPSCs exist for many neurodegenerative diseases. These cells have the benefit of being able to be made from patient cells. Initially, fibroblasts were used but now other cell types can be used, including the easily accessible PBMCs [51]. They can also be manipulated with gene manipulation technology, such as CRISPR, and therefore can model both sporadic and genetic forms of the diseases. During the creation of iPSCs and their subsequent induced differentiation into other cell types, genetic changes can occur, so care must be taken to screen them for major genetic rearrangements. However, smaller genetic changes are not so easily detected, so the possibility of their occurrence should be borne in mind [52]. Observing the same outcomes in multiple, independent iPSC lines can mitigate the risk of misleading results. Another important factor to keep in mind is that

creating iPSCs requires the progenitor cells to be reprogrammed, and this is achieved by expression of several transcription factors which induce and maintain the pluripotent state [53]. The epigenetic modifications are removed and, as many neurodegenerative diseases seem to be caused by a mixture of genetics and environment, this may be a limitation of these cell lines for studying these disorders. The generation of iPSCs and differentiation into neuronal cell types and other cell types is still currently an expensive, laborious process which is out of the reach of many laboratories. However, the technologies associated with these cell lines are improving at a rapid rate and suggest that the cost and time involved will be reduced in the not-so-distant future.

An alternative to these cell models is the transfection of PBMCs with Epstein–Barr virus (EBV) to generate continuously proliferating lymphoblastoid cell lines (LCLs). EBV selectively infects resting B cells, activates them and establishes a latent infection. The EBV genome has been reported to exist in these cells as distinct episomes, and the number of copies of the EBV genome was reported in a study of just under 1000 LCLs from the 1000 genomes project to be in the range of 20–29 [54]. Lymphoblastoid cell lines express several EBV proteins, and EBNA2 (EBV encoded nuclear antigenic protein) and LMP1 (latent infection membrane protein) have been shown to be essential in cell immortalisation, along with other latent phase EBV proteins. EBNA2 is a transcription factor that modulates expression of both viral and host genes, while LMP1 mimics a constitutively active CD40 to activate nuclear factor kB (NF-kB) [55]. Together, the EBV proteins promote B cell activation, cell proliferation and virus latency.

As the virus exists in LCLs as an episome and expresses only a few viral proteins, there is minimal change to the host genome. Comparison of lymphoblastoid cell lines to their progenitor lymphocyte cells shows that the genomes are very similar with minimal difference between the two (99% similarity [56]). There is an increase in mtDNA copy numbers and also in mitochondrial mass, presumably in response to the cells transforming from resting cells into actively proliferating cells. The higher mitochondrial content makes the cells more oxidative than other cell types, such as fibroblasts, and as such, subtle differences in mitochondrial respiration are more likely to be detected in these cells. The somatic mutation rate is low (reported at 0.3% mutations per genome [57]) making them well suited to continuous culture in the laboratory setting. As the cells are transformed from resting cells into actively proliferating cells, many changes to gene expression occur to accommodate this, such as alterations in the levels of signalling proteins associated with activation, receptor activity and inflammation, cell cycle and metabolism. Whilst there are many changes in expression, the magnitude of the change is not large with one study reporting only 0.003% of transcripts with a magnitude change of 1.5-fold or higher [58]. Changes in methylation patterns are also observed with a general decrease in methylation levels in LCLs compared to B cells, as one might expect from cells that are actively proliferating and so need to be transcriptionally active. Despite these obvious differences, the methylation pattern and gene expression profiles of lymphocytes are largely maintained in LCLs and display many of the specific characteristics of primary B cells [58]. This is also true for many diseases, and clear differences in the transcriptomes and the epigenomes of patients and controls have been identified in LCLs for numerous diseases [59][60][61][62][63]. LCLs are increasingly being used as models of disease and given their high oxidative nature, are ideal systems for studying mitochondrial function. Many large facilities and biobanks now store large collections of LCLs from various disease and control groups in preference to other material, such as PBMCs (www.ecacc.org.uk;

www.alspac.bris.ac.uk; http://cimr.umdnj.edu; www.lgcpromochem-atcc.com; www.rutgers.edu; www.coriell.org; access on 1 April 2021) [64]. LCLs were also used to provide the DNA for the 1000 genomes project.

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