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Review

FISHing for Unstable Cellular Genomes in the Human Brain

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Abstract

The human brain has been repeatedly shown to exhibit intercellular/somatic genomic variations at the chromosomal level, which are involved in the neuronal diversity in health and disease. Brain-specific chromosomal mosaicism (aneuploidy) and chromosome instability play a role in the normal and pathological neurodevelopment, neurodegeneration and aging of the central nervous system. Regardless of achievements in somatic cell (single-cell) genomics, there is still no consensus on the amounts of chromosomally abnormal cells in the normal and diseased brain. Actually, the results of single-cell whole genome analysis seem to be different from molecular neurocytogenetic data obtained by fluorescence *in situ* hybridization (FISH). In this context, a review of FISH-based approaches to chromosomal mosaicism/instability in single neural cells appears to be important in the so-called post-genomic era. Looking through the literature highlighting the patterns of chromosomal mosaicism/instability in the diseased human brain, we have found that FISH-based techniques for studying interphase chromosomes represent a unique methodology for

uncovering structural and behavioral genome changes in single neural cells. More importantly, interphase FISH techniques applied for molecular neurocytogenetic analysis are not interchangeable (i.e. each one is developed to solve a specific task). Therefore, it is highly likely that molecular neurocytogenetic studies will benefit from the application of FISH, leading to discoveries of neurogenomic mechanisms of human neuronal diversity and brain diseases.

Keywords
Aneuploidy; brain; chromosome instability; fluorescence *in situ* hybridization; somatic mosaicism

1. Introduction

The studies of chromosomes within the central nervous system have long been recognized as an important part of neuroscience and genetic research [1, 2]. A growing body of research on chromosomal variations in the human brain forms the theoretical and empirical basis of the emerging field of molecular neurocytogenetics [3]. Currently, intercellular genome variations at the chromosomal level are generally accepted to be a causative mechanism for brain diseases and neuronal diversity [4, 5]. Taking into account the immense diversity of neuronal cells populating the human brain [6], it is not surprising that somatic mosaicism has become the focus of molecular cytogenetics and genomics [7-9]. Furthermore, somatic changes of the cellular genome occur throughout the ontogeny, being implicated in development and aging [10, 11]. Apparently, the human central nervous system is also affected by the ontogenetic genomic/chromosomal variations despite the post-mitotic nature of brain cells [3, 10]. Regardless of the achievements in molecular neurocytogenetics, the questions surrounding the way to uncover chromosomal abnormalities in single cells remain unanswered [3, 12, 13]. More precisely, whole genome scan data (including data of single-cell analyses) are matched against those obtained by molecular cytogenetic visualization techniques (i.e. fluorescence *in situ* hybridization or FISH) [3, 12-14]. In light of this problem, we have suggested that a review dedicated to molecular cytogenetic aspects of studying cellular genomes in the human brain is required.

2. Single-Cell Molecular Cytogenomic Analyses of the Human Brain

Somatic mosaicism seems to possess specific effects on brain development and function. A genetically abnormal neuron may form up to ten thousand connections with other neurons altering their functions. This ability of neuronal cells has been suggested to underlie the effect of somatic genome variations (mainly, aneuploidy) on brain function in health and disease [1, 5, 15]. Since aneuploidy involves from hundreds to thousands of genes, such genomic variations can dramatically alter cellular homeostasis [16-18]. Thus, there is a strong theoretic background for uncovering genomic variations in single brain cells or, in other words, molecular neurocytogenetic research.

FISH-based molecular cytogenetic studies revealed the developing brain to be the fetal tissue featured by confined chromosomal mosaicism. The developing human brain was additionally

featured by chromosome instability or sporadic aneuploidy affecting more than 30% of cells [19-21]. In the adult brain, aneuploidy seemed to affect up to 10% of cells [22-26]. Interestingly, the rate of decrease in cellular populations of the brain during the early ontogeny correlated with the rate of decrease in the amount of aneuploid cells in the developing human central nervous system, allowing for the speculations about the role of chromosomal instability/aneuploidy in regulating cellular populations in the human brain [6, 10, 17, 20, 27]. These ontogenetic genomic variations were later considered an empirical basis for designing forthcoming studies of somatic mosaicism in the human brain [27-29]. However, since single-cell genome scanning techniques demonstrated <3% of aneuploidy cells in the normal adult human brain [14, 21, 26, 30], addressing technological aspects of molecular neurocytogenetics were required.

Somatic mosaicism is recognized as a genetic mechanism for a variety of brain diseases [7, 15, 31, 32]. More importantly, somatic mosaicism and genome (chromosome) instability mediates neurodegeneration [25, 33-35], suggesting that these phenomena are a molecular link between neurodegeneration, cancer and aging [25, 36]. In this context, it is to mention that the contribution of somatic mosaicism and chromosome instability to brain aging remains a matter of conjecture, mainly due to data differences between single-cell whole genome analysis and molecular cytogenetic studies [37-40].

At the beginning of molecular neurocytogenetics, observations demonstrating functional activity and integration of genomically abnormal neurons into brain circuitry suggested brain specific chromosomal mosaicism/instability as a mechanism for psychiatric and neurological disorders (for more details, see [41]). Thus, schizophrenia and comorbid psychiatric disorders were associated with mosaic aneuploidy [42-44], chromosome-1-specific instability [43] and brain-specific copy number variations [45] in a significant proportion of cases. Appreciable number of autism cases was suggested to be also associated with mosaic aneuploidy [46, 47]. These findings were recently used for proposing a cytogenomic hypothesis, which suggested behavioral variability to be mediated by fluctuations of somatic mosaicism rates [48]. Probably, interphase chromosome breaks, which are exclusively uncovered by FISH-based molecular neurocytogenetic approaches, might contribute to the behavioral changes highlighted in the cytogenomic hypothesis.

Alzheimer's disease was also repeatedly associated with high rates of mosaic aneuploidy (for more details, see [23, 24, 33, 49]). For instance, the Alzheimer's disease brain exhibited high rates of X chromosome aneuploidy, which suggest a link between brain aging (aging is commonly associated with X chromosome aneuploidy) and this devastative neurodegenerative disorder [50]. The disorder was also associated with regional mosaic genomic heterogeneity [51] and chromosome/genome instability [24, 52, 53]. However, single-cell genomic analyses questioned the amount of aneuploidy cells in the Alzheimer's disease brain [14]. Additionally, aneuploidization was shown to be likely involved in the pathogenesis of Lewy body diseases [54] and frontotemporal lobar degeneration [55]. Finally, the aforementioned neurocytogenetic discoveries appeared to be important for developing therapeutic strategies for brain dysfunction [56], molecular diagnostic approaches to brain pathology [28, 57, 58], and unraveling molecular and cellular pathways for mental illness [3, 17, 52, 58, 59]. In total, single-cell molecular cytogenomic analyses of the human brain are an important part of current biomedicine. The following part is dedicated to advantages/disadvantages of FISH-based approaches and their possible applications in the post-genomic era.

3. Molecular Neurocytogenetics: Technological Issues

Technological aspects are hard to overestimate in reviewing neurocytogenetic studies. The development of FISH-based approaches to the visualization of specific chromosomal regions or whole interphase chromosomes in their integrity during all stages of the cell cycle has initially launched the molecular neurocytogenetic analysis of the human central nervous system (for more details, see [20, 22, 24, 25]). Alternative platform for studying brain specific intercellular genomic variations in the brain is based on newly developed techniques of single-cell whole-genome analysis by next-generation sequencing (for more details, see [14, 21, 30]). Since the latter platform is generally recognized to be superior to single-cell molecular cytogenetic (microscopic) analysis, there is a need for consistent re-evaluation of the role FISH-based approaches play in single cell genomics.

Although molecular genetic techniques are able to uncover mosaic chromosomal abnormalities and copy number variations in whole fractions of DNA isolated from large cellular populations [4, 13, 27, 60], molecular (interphase) cytogenetic techniques offer numerous additional opportunities for singe-cell chromosomal analysis (for more details, see [12, 61]). It is important to mention that a number of molecular cytogenetic FISH-based methods have been the results of technological developments in molecular neurocytogenetics [3, 61].

Initially, molecular cytogenetic studies were technologically based on multiprobe FISH with chromosome-enumeration DNA probes [1, 15, 19]. Unfortunately, human brain cells exhibit specific nuclear organization referred to high rates of interphase chromosome associations [1, 22], which are not discriminated by multiprobe FISH. To solve this problem, quantitative FISH (digital quantification of FISH results allowing the differentiation between chromosome loss and chromosomal associations) may be applied [62]. Multiprobe FISH with quantitative FISH are unable to depict the whole interphase chromosome in its integrity [12, 61]. To see an interphase chromosome in its integrity and in any cell type with molecular resolutions, interphase chromosome-specific multicolor banding has been developed [22, 63]. This is the only visualization (microscopic) technique offering the possibility to detect interphase chromosome instability without unbalanced genome changes (i.e. chromosomal breaks, fragility etc.) [25, 61]. Despite possibilities for detecting recurrent DNA break clusters [64], a comprehensive alternative to interphase chromosome-specific multicolour banding for uncovering all types of chromosomal instability does not exist.

As it was already mentioned, data on brain-specific aneuploidy obtained by molecular (interphase) cytogenetic techniques are appreciably different from those obtained by single-cell molecular genetic methods. Interphase FISH approaches to molecular cytogenetic analyses of the human brain have high cell scoring potential (more than 5,000-10,000 interphase nuclei per sample/probe set) [1, 4, 8, 61]. However, these techniques are unable to uncover whole spectrum of genomic variations detectable by single-cell next-generation sequencing. The latter, on the other hand, has very low cell scoring potential (i.e. less than 100 cells per sample) [21, 30]. High cell scoring significantly contributes to the success of molecular neurocytogenetic studies, because aneuploid brain cells are extremely rare in cases of chromosome-specific aneuploidy [19-24]. In addition, it is to note that interphase FISH is not free from false-positive/false-negative artifacts produced by unusual signal appearance due to specific nuclear chromosome organization [1, 3, 22]. As mentioned before, to solve this problem, interphase cytogenetic approaches to

chromosome instability in the human brain appear to require the application of quantitative FISH and interphase chromosome-specific multicolor banding.

There are several disadvantages leading to false-positive/false-negative results of both molecular (interphase) cytogenetic (for review, see [1-5]) and single-cell whole-genome scanning techniques (i.e. impossibility to correlate the results of whole genome amplification and the true genome variations in a cell; moderate/low cell scoring potential; for more details, see [3-5, 13]). Accordingly, the rationale for successful analysis of genomic variations in the human brain is to combine data acquired by FISH-based techniques with whole-genome data on individual cells or whole fraction of DNA isolated from large cellular populations. Table 1 summarizes the molecular neurocytogenetic findings and technological issues.

Table 1 Molecular neurocytogenetic findings in the technological context.

Methods	Findings	Advantages	Disadvantages	Refs
Multiprobe FISH	Aneuploidy have been shown to affect cell populations in the normal human; single cases of devastative brain diseases exhibited high rates of aneuploidy have been reported	The possibility to study specific chromosomal loci in interphase nuclei of the human brain is offered	Single chromosomal loci are only visualized; specificity of intranuclear spatial chromosome arrangement (i.e. chromosomal associations) are not discriminated; false-positive monosomies may be reported	[19, 23, 42]
Multiprobe FISH + Quantitative FISH	Aneuploidy rates have been narrowed; additional cases of brain-specific aneuploidy have been reported	A number of types of intranuclear spatial chromosome arrangement (i.e. chromosomal associations) are discriminated; false-positive monosomies are discriminated, as well	Single chromosomal loci are only visualized/digitalized; integral view of an interphase chromosome is not possible	[20, 24, 25, 43, 44, 46, 47, 50, 62]
Interphase chromosome-specific multicolour banding	Aneuploidy, structural chromosome imbalances and instability (i.e. interphase chromosomal breaks)	Interphase chromosomes are visualized in their integrity at molecular resolutions; specificity of	Cell scoring potential is lower as to multiprobe FISH + quantitative FISH; defining interphase chromosome structure requires	[20, 22, 24, 25, 43, 50, 63]

	have been shown to affect the diseased human brain; aneuploidy rate in the unaffected human brain have been found to be lower than previously estimated by multiprobe FISH	intranuclear spatial chromosome arrangement poorly affects study results	sophisticated visual and digital analyses	
Single-cell genome scanning techniques (i.e. next generation sequencing)	Large-scale genomic variations manifesting as chromosomal and/or subchromosomal imbalances have been shown to be less common in the unaffected human brain than previously estimated by FISH-based techniques; however, these variations does affect the human brain	Whole cellular genome is addressed at the highest resolution possible	Cell scoring potential is unacceptably low for scoring rare cells affected by chromosome instability/imbalances or aneuploidy	[21, 26, 30]

4. Conclusions and Future Prospects

The applications of FISH-based methods to molecular neurocytogenetic purposes are not limited to detecting chromosomal abnormalities, inasmuch as these may uncover chromosome instability and behavior that are undetectable by single-cell molecular genetic techniques. Even in the post-genomic era, FISH remains an important methodology for human genome analysis [65]. Despite a number of unresolved disadvantages, the resolution of single-cell whole-genome analysis by next-generation sequencing defines this platform as an efficient tool for studying neuronal genomes. In light of this, one can suggest that there is a need for developing a technique that combines microscopic FISH-based methods with single-cell whole-genome scan. Still, multilateral analysis of neuronal genome behavior at the chromosomal level cannot be appropriately performed without the application of FISH-based technologies. To this end, we suggest that further studies dedicated to uncovering instable cellular genomes in the brain should be targeted on identification of the causes and consequences using post-genomic (empirical and bioinformatic) techniques and molecular cytogenetic methods. These data is applicable for understanding mechanisms and discovering new therapeutic targets in brain diseases.

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Author Contributions

YBY, SGV, and IYI conceived the underlying ideas and basics of molecular neurocytogenetics. IYI wrote the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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