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The applicability of interphase chromosome-specific multicolor banding (ICS-MCB) for studying neurodevelopmental and neurodegenerative disorders[1]

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Abstract

Background: Interphase chromosome-specific multicolor banding (ICS-MCB) has been developed for studying whole chromosomes in interphase nuclei at any stage of the cell cycle at molecular resolution. Previously, important biomedical discoveries have been made using the technique. In the postgenomic era, a need appears to exist for a reevaluation of molecular cytogenetic techniques, including ICS-MCB, which seems to take a well-deserved place. **Aim of the study**: The aim of the present study is to address the applicability of ICS-MCB for studying neurodevelopmental and neurodegenerative disorders. **Conclusions**: A brief overview of previous ICS-MCB applications demonstrates that the technique may provide an appreciable amount of unique data on chromosome abnormalities and organization in interphase nuclei. Furthermore, the technique offers opportunities for evaluating these phenomena in the diseased human brain. Such opportunity seems to be critical for unraveling molecular and cellular mechanisms of neurodevelopmental and neurodegenerative disorders. Therefore, we conclude that ICS-MCB may represent an important part of molecular and cellular studies of neurodevelopmental and neurodegenerative disorders.

Keywords: chromosome; chromosome instability; interphase nucleus; neurodegenerative disorders; neurodevelopmental disorders

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Introduction. Neurodevelopmental and neurodegenerative disorders have been systematically associated with genomic variations (i.e. chromosome abnormalities, copy number variations and single-gene mutations) [1-4]. Besides, genomic variations are commonly mosaic. Furthermore, somatic mosaicism is likely to be an important genetic mechanism for brain diseases. The most common types of somatic genomic variations are chromosomal mosaicism and instability [1, 3, 5-7]. However, despite these observations, somatic chromosomal mosaicism is still under observed. This is more likely because of unacceptable neglect to techniques available for studying intercellular genome variability [1, 7]. Fortunately, molecular cytogenetics does provide approaches towards studying genome variations at chromosomal level [8, 9]. Probably, the most important molecular cytogenetic technique for studying chromosomes in individual cells is interphase fluorescence in situ hybridization (FISH) [10]. The latter has been already shown to provide valuable data on chromosomal mosaicism and the contribution to brain pathology in neurodevelopmental and neurodegenerative disorders [7, 11, 12]. Currently, FISH still represents an important technology for studying chromosomal imbalances and chromosome organization in interphase nuclei regardless of the introduction of post-genomic technologies (i.e. next-generation sequencing and microarray-based methods) [10, 13-15]. The present communication pays attention to a FISH-based technique for studying individual interphase chromosomes in their integrity in single cells – interphase chromosome-specific multicolor banding (ICS-MCB) – and to the applicability for studying neurodevelopmental and neurodegenerative disorders.

ICS-MCB applications.ICS-MCB is a method combining interphase FISH and multicolor chromosomal banding (a FISH-based approach toward banding several chromosomal regions and subregions smaller than a chromosome arm through the use of microdissected DNA probes). The application of ICS-MCB on human cellular nuclei provides the depiction of homologous interphase chromosomes in their integrity at molecular resolution (see Iourov et al. [16, 17]). Actually, there is no true alternative to this technique for studying human interphase chromosomes in their integrity in individual cells [7, 10, 18]. Previously, ICS-MCB has been applied to identify chromosomal abnormalities and instability in the diseased human brain. Furthermore, the technique might be used for determining nuclear chromosome organization in almost all human tissues.

Somatic chromosomal mosaicism and chromosome instability has been repeatedly associated with neurodevelopmental and neurodegenerative disorders [1, 7, 19, 20]. More importantly, these types of genomic variability may be confined to the diseased brain. The phenomenon of brain-specific chromosomal mosaicism seems to play a significant role in the etiology of neurodevelopmental and neurodegenerative disorders [3, 7, 19, 21]. For instance, chromosomal instability, a process closely related to cancerization, has been uncovered to mediate neurodegeneration using ICS-MCB. Interphase chromosome breaks (ICB) have been found to be the commonest type of chromosomal instability mediating cerebellar neurodegeneration in ataxia-telangiectasia [22]. ICB are currently undetectable by any type of molecular (cytogenetic) techniques apart from ICS-MCB. Brain-specific aneuploidy and copy number variations have

been shown to be implicated in molecular and cellular pathways neurodegeneration [3, 19, 23]. Aneuploidy of chromosomes 21 and X uncovered by ICS-MCB has been found to be a common mechanism for Alzheimer's disease, one of the commonest neurodegenerative diseases in elderly persons [24-26]. Currently, such types of genomic variability are suggested to be key elements of the Alzheimer's disease pathogenetic cascade [27]. Age-specific chromosomal mosaicism requires to be addressed by high-resolution single-cell molecular cytogenetic techniques (i.e. ICS-MCB) [28, 29]. Finally, chromosomal instability (chromothripsis) appears to mediate brain dysfunction in neurodevelopmental and neurodegenerative disorders [30]. In total, the phenomena identified using ICS-MCB have been recognized as genomic mechanisms of intercellular genetic variation in health and disease [31, 32].

Alternatively, ICS-MCB may be applied for studying chromosome arrangement in interphase nuclei [3, 10, 16, 17, 21]. It is to note that positioning of chromosomes in the nucleus and its impact on transcriptional genome activity and genome stability maintenance have not been evaluated in the majority of human tissues. The application of ICS-MCB would be certainly valuable to fill this gap in our biomedical knowledge. It is highly likely that chromosome nuclear organization is specific for a variety of brain diseases including those leading to neurodevelopmental and neurodegenerative disorders.

Taking into account previous experience, one may define a spectrum of targets for molecular (neuro) cytognetic studies of neurodevelopmental and neurodegenerative disorders using ICS-MCB. Figure schematically shows these ICS-MCB targets.

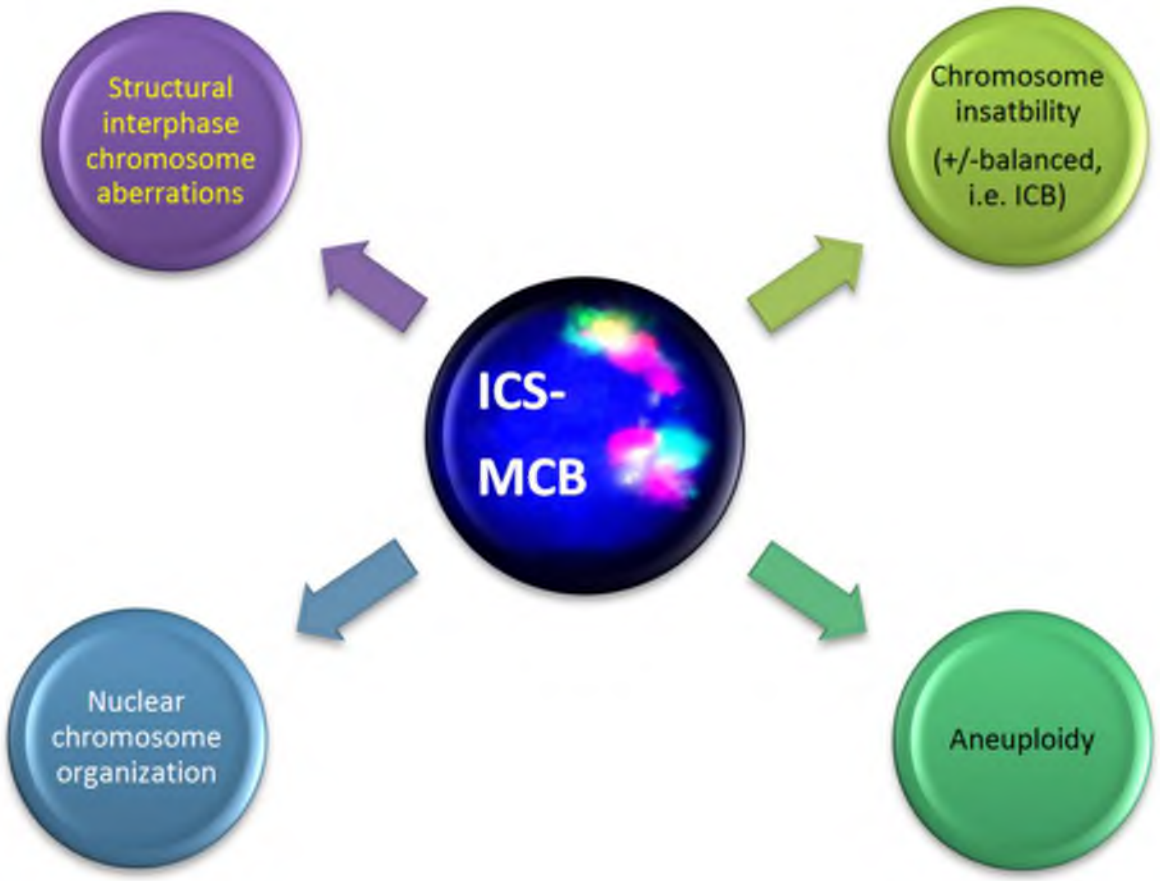

Fig. Targets of ICS-MCB in molecular (neuro) cytognetic studies of neurodevelopmental and neurodegenerative disorders (ICS-MCB depiction is from Yurov et al. [26]; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0)

The spectrum of ICS-MCB targets evidences for high applicability of this molecular cytogenetic technique for studying brain diseases. Recently, neurodevelopmental and neurodegenerative disorders have been shown to be mediated by a complex pattern of genetic-environmental interactions. It is more probable that chromosomal abnormalities/instability (i.e. aneuploidy and ICB) are important elements of the pathogenetic cascade. In other words, environmental effects interact with specific genomic susceptibility to the instability to cause aneuploidy and ICB [33]. Nuclear chromosome organization might be implicated in pathways to neurodevelopmental and neurodegenerative disorders in a similar way. Therefore, further studies aimed at determination of molecular and cellular pathways to neurodevelopmental and neurodegenerative disorders would benefit from the application of ICS-MCB.

Conclusions. The evaluation of ICS-MCB applicability shows this technique to offer a unique possibility to address chromosomal instability and nuclear chromosome organization in human interphase nuclei. Since the overwhelming majority of human cells are likely to be in interphase, ICS-MCB represents an important tool for chromosomal and genomic research. In summary, complementary surveys of molecular and cellular (genetic and genomic) mechanisms of neurodevelopmental and neurodegenerative disorders are likely to require this interphase cytogenetic approach to chromosomal analysis.

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