Integrated Genome Regulation of Brain Development: Targeting Ontogenomic Networks in Schizophrenia via Nanomachine-Genome Optical Communications

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ABSTRACT

Major breakthroughs in the field of genomics, embryonic stem cell (ESC) biology, optogenetics and biophotonics are enabling the control and monitoring of biological processes through light. By incorporating light-actuated/light-emitting proteins into cells, key biological processes at the sub-cellular level can be controlled and monitored in real time. This article describes a new type panontogenic, i.e., affecting the entire ontogeny or development of an individual organism from its earliest stage to maturity, regulation of the developmental genome and the perspective for its control with nanomachines through optical communication.

CCS CONCEPTS

• **Human-centered computing → Human computer interaction (HCI)**; • **Hardware → Biology-related information processing**; • **Networks**;

KEYWORDS

Genomics, Nanophotonics, Brain Machine Interfaces, Nanonetworking

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1 INTRODUCTION

Construction of a complex functional system, such as a living organism, requires not only raw building materials but also an assembly program, organized into flexible feedback and feed-forward subroutines that can function within, and readily adapt to a nonstable environment [6]. Like the general ontogeny, construction of the Nervous System uses two sources of information: stable "genomic blueprint" which has developed over a billion of years of evolution and highly variable environmental "extragenomic" signals, i.e., initiated outside the genome. Yet with every new generation one observes a successful reconstruction of an organism with relatively

infrequent errors. To understand how the ontogenic (developmental) fidelity is ensured we investigated the mechanisms and the principles which operate at the interface of genomic and extragenomic information [7]. The central factor in this regulation appears to be a nuclear form of the FGFR1 gene encoded protein. Genetic experiments have placed the FGFR1 (Fibroblast Growth Factor Receptor 1) gene on the top of the gene hierarchy that governs gastrulation, development of the major body axes, nervous system, muscles, and bones, by affecting downstream genes that control the cell cycle, pluripotency and differentiation, as well as microRNAs [5].

2 RESULTS

Studies carried out in our laboratory demonstrated that the regulatory control exerted by INFS (Integrative Nuclear FGFR1 Signaling) is due to the nuclear isoform of FGFR1 (nFGFR1), which integrates signals from development-initiating factors and operates at the interface of genomic and epigenomic information. nFGFR1 cooperates with a panoply of transcription factors, and targets thousands of genes encoding mRNAs, as well as regulatory micro RNA (miRNAs) in critical ontogenic networks. Experiments utilizing pluripotent stem cells, capable of developing into all cells of the body, and cerebral organoids, mini-brains like structures that mimic developing human brain, revealed a new panontogenic mechanism, INFS, which underwrites the environmental genome programming during development4. nFGFR1 targets promoters of the ancient proto oncogenes and tumor suppressor genes, which when altered by mutation, can contribute to cancer. nFGFR1 regulates the pluripotency core genes as well as metazoan morphogens that delineate body axes, construct the nervous system and the mesodermal and endodermal tissues. Globally, during neuronal development, the nFGFR1 regulates coordinate gene networks by determining both the number of correlated genes and the extent of their correlation. This panontogenic genome programming by INFS feed-forward and feedback loops expands our understanding of ontogeny and has inspired new search for the roots of developmental diseases like schizophrenia, autism or cancer [5].

Studies of induced pluripotent stem cells (iPSCs) dedifferentiated from the skin fibroblasts of schizophrenia patients and control individuals revealed that the disorder is programmed at the preneuronal stage, involves a common dysregulated set of genes, mRNA transcriptome, and identified INFS as a common dysregulated mechanism [3]. We used iPSC derived cerebral organoids from controls and schizophrenia patients to model the first trimester of the human brain development [4]. The schizophrenia organoids revealed an abnormal scattering of proliferating Ki67+Neural Progenitor Cells (NPC) from the ventricular zone, throughout the sub-cortical and cortical zones, regions of the developing human brain or cerebral organoids. TBR1 pioneer neurons and reelin, which guide cortico-petal migration, towards the brain cortex, were restricted from the schizophrenia cortex. The maturing neurons were abundantly developed in the subcortical regions, but were depleted from the schizophrenia cortex. The decreased intracortical connectivity was denoted by changes in the orientation and morphology of the cortical interneurons expressing calcium-binding protein, calretinin. In schizophrenia organoids, nFGFR1 was depleted from the developing cortical neurons while it was present in deep subcortical Neural Progenitor cells. Global genome analyses revealed a widespread disruption of the neuro-ontogenic gene networks in the underdeveloped cortical neurons stemming from the reduced nFGFR1 signaling [3, 4]. These studies showed for the first time, the nature and the progression of the cortical maldevelopment in schizophrenia and linked it to altered INFS. Targeting INFS holds new promise for the preventive treatment of schizophrenia, reconstructive medicine and cancer therapy. Towards this goal we are designing light controlled molecular switches in which 650 nm laser light reconstitutes the transcriptional TET/VP16 complex in order to reactivate the nFGFR1 expression specifically in the developing organoid cortex.

3 PERSPECTIVE

Our ongoing work entails testing whether nano-laser [1, 2] induced nFGFR1 could correct development of the brain cortex and dysregulated gene networks in schizophrenia. These proof of concept experiments could open new avenue for the treatment of human diseases using nanophotonic devices.

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