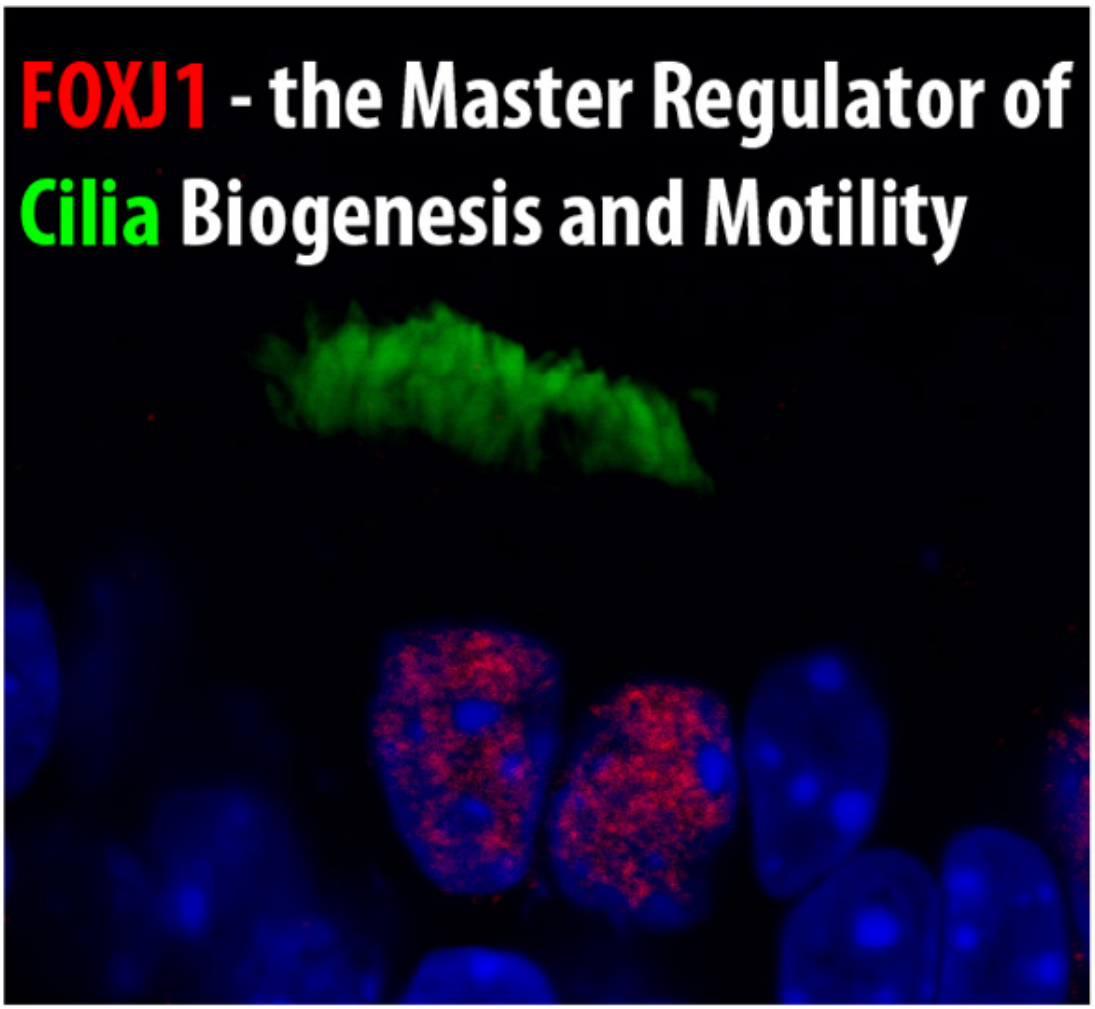
Identification of Important Effector Proteins in the FOXJ1 Transcriptional Network Associated With Ciliogenesis and Ciliary Function

Wednesday, 13 Mar 2019



Ishita Mukherjee[1], Sudipto Roy[2,3,4*], and Saikat Chakrabarti[1*]

1Council for Scientific and Industrial Research (CSIR) - Indian Institute of Chemical Biology (IICB), Structural Biology and Bioinformatics Division, Translational Research Unit of Excellence, Kolkata, West Bengal, India

[2]Institute of Molecular and Cell Biology, Proteos, Singapore

[3]National University of Singapore, Department of Paediatrics, Yong Loo Lin School of Medicine, Singapore

[4]National University of Singapore, Department of Biological Sciences, Singapore

***Correspondence:**

Saikat Chakrabarti; saikat@iicb.res.in

Sudipto Roy; sudipto@imcb.a-star.edu.sg

Published in: ***Frontiers in Genetics***
New Approaches to Study Ciliopathies and Centrioles-Related Genetic Disorders on 01 March 2019

https://doi.org/10.3389/fgene.2019.00023

Abstract

Developmental defects in motile cilia, arising from genetic abnormalities in one or more ciliary genes, can lead to a common ciliopathy known as primary ciliary dyskinesia (PCD). Functional studies in model organisms undertaken to understand PCD or cilia biogenesis have identified hundreds of genes regulated by FOXJ1, the master regulator of motile ciliogenesis. However, limited systems based studies have been performed to elucidate proteins or network/s crucial to the motile ciliary interactome, although this approach holds promise for identification of multiple cilia-associated genes, which, in turn, could be utilized for screening and early diagnosis of the disease. Here, based on the assumption that FOXJ1-mediated regulatory and signalling networks are representative of the motile cilia interactome, we have constructed and analysed the gene regulatory and protein-protein interaction network (PPIN) mediated by FOXJ1. The predicted FOXJ1 regulatory network comprises of 424 directly and 148 indirectly regulated genes. Additionally, based on gene ontology analysis, we have associated 17 directly and 6 indirectly regulated genes with possible ciliary roles. Topological and perturbation analyses of the PPIN (6927 proteins, 40,608 interactions) identified 121 proteins expressed in ciliated cells, which interact with multiple proteins encoded by FOXJ1 induced genes (FIG) as important interacting proteins (IIP). However, it is plausible that IIP transcriptionally regulated by FOXJ1 and/or differentially expressed in PCD are likely to have crucial roles in motile cilia. We have found 20 de-regulated topologically important effector proteins in the FOXJ1 regulatory network, among which some (PLSCR1, SSX2IP, ACTN2, CDC42, HSP90AA1, PIAS4) have previously reported ciliary roles. Furthermore, based on pathway enrichment of these proteins and their primary interactors, we have rationalized their possible roles in the ciliary interactome. For instance, 5 among these novel proteins that are involved in cilia associated signalling pathways (like Notch, Wnt, Hedgehog, Toll-like receptor etc.) could be 'topologically important signalling proteins'. Therefore, based on this FOXJ1 network study we have predicted important effectors in the motile cilia interactome, which are possibly associated with ciliary biology and/or function and are likely to further our understanding of the pathophysiology in ciliopathies like PCD.

Figure:

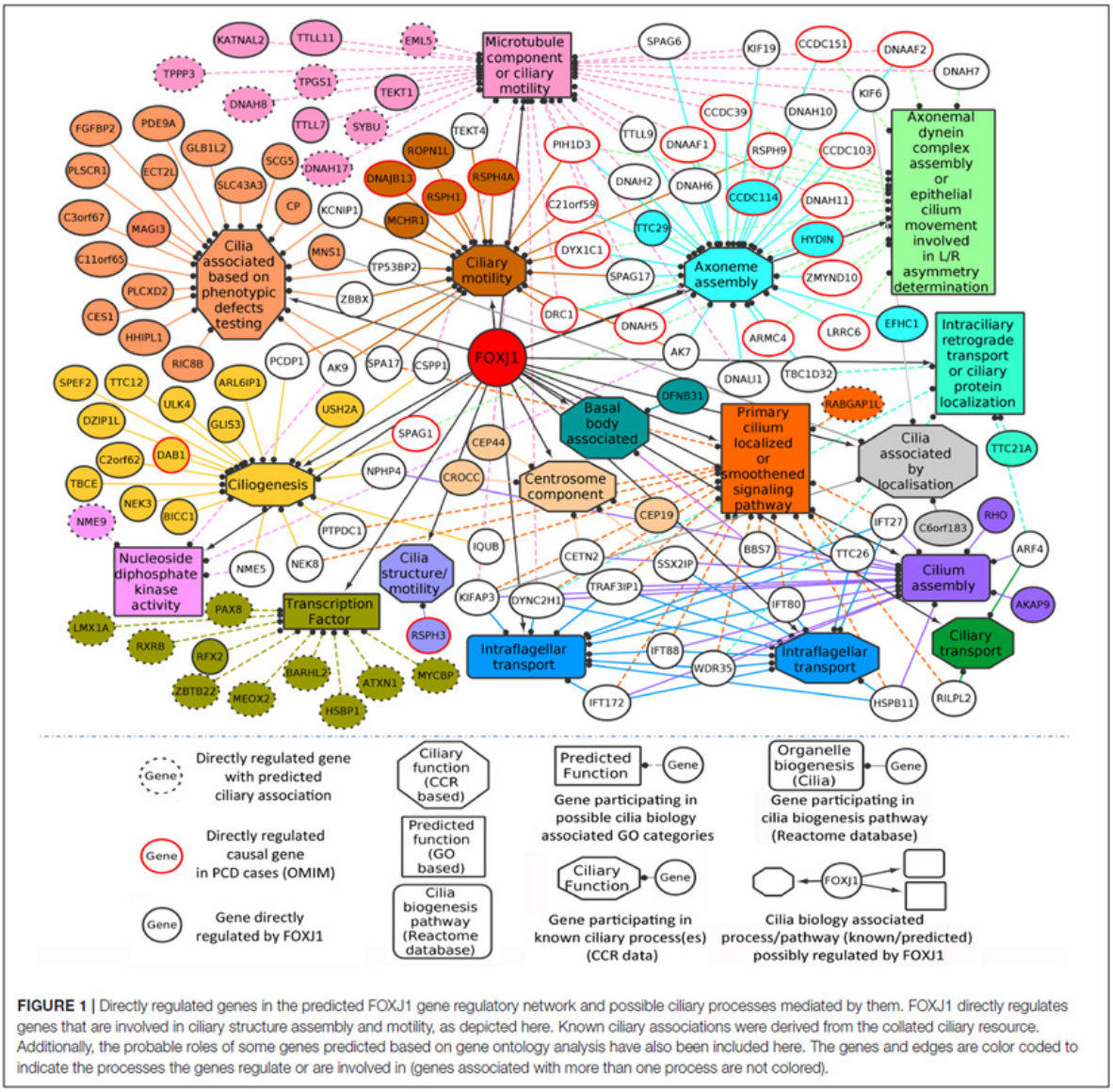


FIGURE 1 | Directly regulated genes in the predicted FOXJ1 gene regulatory network and possible ciliary processes mediated by them. FOXJ1 directly regulates genes that are involved in ciliary structure assembly and motility, as depicted here. Known ciliary associations were derived from the collated ciliary resource. Additionally, the probable roles of some genes predicted based on gene ontology analysis have also been included here. The genes and edges are color coded to indicate the processes the genes regulate or are involved in (genes associated with more than one process are not colored).