Molecular and Cellular Neuroscience xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Molecular and Cellular Neuroscience

journal homepage: www.elsevier.com/locate/ymcne

Nervous system development and disease: A focus on trithorax related proteins and chromatin remodelers

Amanda Moccia[a], Donna M. Martin[a,b,*]

[a] Department of Human Genetics, The University of Michigan Medical School, Ann Arbor, MI 48109, United States
[b] Department of Pediatrics and Communicable Diseases, The University of Michigan Medical School, Ann Arbor, MI 48109, United States

ARTICLE INFO

Keywords:
Trithorax
Chromatin
Neurodevelopment
Disease

ABSTRACT

The nervous system comprises many different cell types including neurons, glia, macrophages, and immune cells, each of which is defined by specific patterns of gene expression, morphology, function, and anatomical location. Establishment of these complex and highly regulated cell fates requires spatial and temporal coordination of gene transcription. Open chromatin (euchromatin) allows transcription factors to interact with gene promoters and activate lineage specific genes, whereas closed chromatin (heterochromatin) remains inaccessible to transcriptional activation. Changes in the genome-wide distribution of euchromatin accompany transcriptional plasticity that allows the diversity of mature cell fates to be generated during development. In the past 20 years, many new genes and gene families have been identified to participate in regulation of chromatin accessibility. These genes include chromatin remodelers that interact with Trithorax group (TrxG) and Polycomb group (PcG) proteins to activate or repress transcription, respectively. Here we review the role of TrxG proteins in neurodevelopment and disease.

1. Introduction

Embryonic development proceeds from a single multipotent cell to a multicellular complex organism with distinct organs, tissues, and cell types that retain their identities over developmental space and time. While some mature cells and tissues exhibit high levels of proliferative and regenerative potential (i.e., skin and gut epithelial cells), others (i.e., neurons) are quiescent and unable to self-renew upon injury. The mechanisms by which specific cell types maintain their fate or "memory" that instructs profiles of gene expression despite active DNA replication and mitosis remain a mystery; however, much work has been done to identify the genes, molecules, and chromatin-associated factors involved in this process. Chromatin structure has a regulatory role on the transcriptional profile on processes that underlie cellular proliferation and maintenance of cell fate. Identifying the molecular pathways that direct chromatin structure and gene expression is a central goal in developmental biology, and has important relevance for understanding basic mechanisms of developmental disorders.

This review explores mechanisms of human developmental disorders caused by pathogenic variants in human homologs of *trithorax* group (TrxG) genes encoding histone methyltransferases, demethylases, and chromatin remodelers (Table 1). TrxG is a family of proteins that form large multi-protein complexes exhibiting histone methyltransferase and/or chromatin remodeling functions (Schuettengruber et al., 2011). Drosophila *trithorax* (*trx*) was first identified as a spontaneous pathogenic variant in flies with abnormalities of head, thoracic, and abdominal structures, consistent with transformations of body segment identity (Ingham, 1983). In the fly, *trx* encodes for a histone methyltransferase and acts to suppress the functions of Polycomb group (PcG) genes. TrxG and PcG genes are highly conserved across evolution, and act antagonistically at genetic targets such as the *Hox* gene cluster to regulate gene expression (Steffen and Ringrose, 2014). In general, PcG genes encode proteins that function as transcriptional repressors, whereas TrxG genes encode proteins that act as transcriptional activators (Fig. 1). This mutual antagonism has led to a model whereby PcG and TrxG proteins switch between stably repressed or activated patterns of gene expression during development.

TrxG proteins generally function as large multi-protein complexes, where they localize to transcription start sites, enhancers, and gene bodies, with variable roles that are influenced largely by their interacting partners and target sites in the genome. Based on their molecular functions, TrxG proteins are categorized into three general classes. The first class of TrxG proteins comprises SET-domain histone methyltransferases. This class includes the COMPASS (complex of proteins associated with Set1) members SET1A, SET1B, and mixed lineage leukemia-1-4 (MLL1, MLL2, MLL3 and MLL4), among others (Piunti and

* Corresponding author at: 8220C MSRB III, 1150 W. Medical Ctr. Dr., Ann Arbor, MI 48109-5646, United States.
E-mail address: donnamm@umich.edu (D.M. Martin).

https://doi.org/10.1016/j.mcn.2017.11.016
Received 30 June 2017; Received in revised form 8 November 2017; Accepted 27 November 2017

Table 1
Human genetic diseases associated with Trithorax group related genes.

Trithorax group class	Gene name	Human disease association	SFARI gene score	SFARI syndromic
Histone methyltransferases	*KMT2F* (*SET1A*)	Association with schizophrenia and neurodevelopmental disorders		
	KMT2A (*MLL1*)	Wiedemann-Steiner syndrome and Leukemia Myeloid	2	S
	KMT2D (*MLL2*)	Kabuki syndrome 1		
	KMT2C (*MLL3*)	Kleefstra syndrome	2	
	KMT2B (*MLL4*)	Dystonia		
Histone demethylase	*KDM6A* (*UTX*)	Kabuki syndrome 2		
ATP-dependent chromatin remodelers - SWI/SNF	*SMARCA1* (*SNF2L*)	Schizophrenia, microcephaly with intellectual disability, Rett-like phenotypes		
	SMARCA2 (*BRM*)	Nicolaides-Baraitser syndrome and schizophrenia	S	S
	SMARCA4 (*BRG1*)	Coffin-Siris syndrome 4 and rhabdoid tumor predisposition syndrome 2		
	SMARCB1 (*SNF5*)	Coffin-Siris syndrome 3, somatic rhabdoid tumors, rhabdoid predisposition syndrome 1, and susceptibility to Schwannomatosis-1		
	SMARCE1 (*BAF57*)	Coffin-Siris syndrome 5, susceptibility to familial meningioma		
	ARID1A (*BAF250A*)	Coffin-Siris syndrome 2		
	ARID1B (*BAF250B*)	Coffin-Siris syndrome 1	1	S
ATP-dependent chromatin remodelers - INO80	*YY1AP1* (*YAP*)	Grange syndrome		
	SRCAP (*SWR1*)	Floating-Harbor syndrome	2	
ATP-dependent chromatin remodelers - CHD	*CHD1*	Pilarowski-Bjornsson syndrome		
	CHD2	Childhood-onset epileptic encephalopathy	2	S
	CHD4	Sifram-Hitz-Weiss syndrome		
	CHD7	CHARGE syndrome	S	S
	CHD8	Autism Spectrum Disorder	1	S

Human disease associations, and autism susceptibility according to SFARI gene classification for Trithorax group related genes. Scoring for SFARI gene is as follows: syndromic (S), high confidence (1), and strong candidate (2).

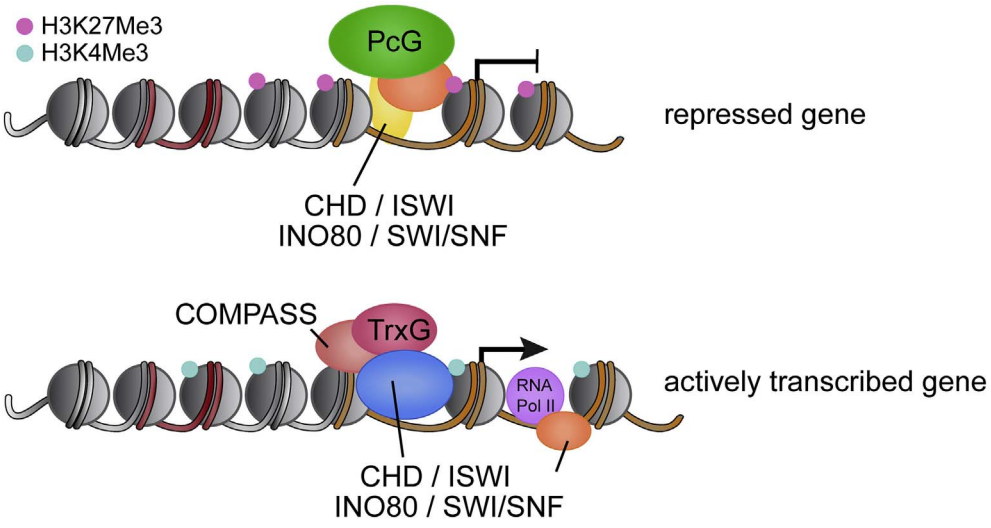

Fig. 1. Schematic of Polycomb and Trithorax related proteins at promoters of repressed and active genes.
Repressed genes are bound by Polycomb group proteins (PcG) whereas Trithorax-related proteins (TrxG) localize to actively transcribed genes. COMPASS (complex of proteins associated with Set1) opposes PcG activity to activate transcription. ATP-dependent chromatin remodelers (CHD, ISWI, INO80, and SWI/SNF) regulate DNA accessibility, which influences gene repression and activation during embryonic development.

Shilatifard, 2016). The second class of TrxG proteins contains ATP-dependent chromatin remodelers that "read" the histone modifications established by SET domain-containing enzymes. This class includes switch/sucrose non-fermenting (SWI/SNF) proteins, imitation switch (ISWI), inositol auxotroph 80 (INO80), and chromodomain-helicase-DNA binding (CHD) proteins. Chromatin remodelers harness the energy of ATP to slide nucleosomes along DNA, evict nucleosomes from DNA, or exchange histone dimers, thereby altering the chromatin architecture and making it more or less accessible to transcription factors and other regulatory proteins or RNA. The third class of TrxG proteins bind specific DNA sequences called TrxG response elements (TREs), which often coincide with PcG response elements (PREs) that switch status between activation and silencing by mechanisms that involve noncoding RNA transcription (Herzog et al., 2014). This general classification of TrxG proteins is still evolving, as new information is obtained about the functions of this large group of proteins and associated factors.

2. Histone modifications and developmental disorders

2.1. Epigenetic mechanisms

Abundant post-translational modifications of histone tails (phosphorylation, methylation, acetylation, ubiquitination, sumoylation), which regulate accessibility of genetic information, are a distinguishing feature of eukaryotic organisms. Epigenetic regulation of gene expression requires involvement of many different histone modifying enzymes, including "writers" that attach modifications to histone tails, and "erasers" that remove modifications, whereas "readers" recognize modifications distributed in a cell-specific manner across the genome. A function of histone modifications is to coordinate chromatin remodelers and transcriptional machinery for transcriptional regulation. Histone modifications function together with histone variants, chromatin-remodeling activities, DNA methylation, and histone chaperones to contribute to the faithful establishment and maintenance of the chromatin