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Review

Epigenetic regulation of female puberty

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ABSTRACT

Substantial progress has been made in recent years toward deciphering the molecular and genetic underpinnings of the pubertal process. The availability of powerful new methods to interrogate the human genome has led to the identification of genes that are essential for puberty to occur. Evidence has also emerged suggesting that the initiation of puberty requires the coordinated activity of gene sets organized into functional networks. At a cellular level, it is currently thought that loss of transsynaptic inhibition, accompanied by an increase in excitatory inputs, results in the pubertal activation of GnRH release. This concept notwithstanding, a mechanism of epigenetic repression targeting genes required for the pubertal activation of GnRH neurons was recently identified as a core component of the molecular machinery underlying the central restraint of puberty. In this chapter we will discuss the potential contribution of various mechanisms of epigenetic regulation to the hypothalamic control of female puberty.

Abbreviations: 5hmC, 5-hydroxymethylcytosine; 5-mC, 5-methylcytosine; Ac, acetyl; ARC, arcuate nucleus; ASH2, absent, small, or homeotic-like 2; AVPV, anteroventral periventricular nucleus; BMAL1/ARNTL, brain and muscle ARNT-like 1/aryl hydrocarbon receptor nuclear translocator-like; BMI1, B lymphoma Mo-MLV insertion region 1 homolog; BPA, bisphenol A; BRCA1, breast cancer 1; CBX, chromobox; CCCs, clock-controlled genes; CCNA, cyclin A2; CDP/CUX1/CUTL1, cut-like homeobox 1; CHD7, chromodomain helicase DNA binding protein 7; CLOCK, clock circadian regulator; COMPASS, complex of proteins associated to Set1; CRC, chromatin remodeling complex; CRY, cryptochrome circadian clock; CXXC1, CXXC finger protein 1; DMN, dorso medial nucleus; DNMTs, DNA methyltransferasess; DYN, dynorphin; E2, estrogen; EAP1/IRF2BPL, enhanced at puberty/interferon regulatory factor 2 binding protein-like; EDCs, endocrine disruptor chemicals; EED, embryonic ectoderm development; endo siRNAs, endo-small inhibitory RNAs; ERa, estrogen receptor alpha; EREs, estrogen responsive elements; EZH1/2, enhancer of Zeste 1 or 2; FGF21, fibroblast growth factor 21; FTO, fat mass and obesity associated; GABA, gamma-aminobutyric acid; Glu, glutamate; GnIH, gonadotropin-inhibiting hormone; GnRH, gonadotropin-releasing hormone; GNRHR, GnRH receptor; GWAS, genome wide association study; H, histone; HATs, histone acetyltransferases; HBP, hexosamine biosynthetic pathway; HCF1, host cell factor C1; HDACs, histone deacetylases; hDPY30, human protein dumpy (Dpy)-30 homolog; HMTs, histone methyltransferases; IGF1, insulin-like growth factor 1; IRX3, iroquois homeobox 3; K, lysine; KDM3B/ JMJD1B, lysine (K)-specific demethylase 3B; KiSS1, gene encoding kisspeptins; KISS1R/GPR54, gene encoding kisspeptin receptor/G-protein coupled receptor 54; KNDy, neurons that produce kisspeptin, neurokinin B and dynorphin; LAMP3, lysosomal-associated membrane protein 3; LEP, leptin; LEPR, leptin receptor; LH, luteinizing hormone; lincRNAs, long intergenic noncoding RNAs; MAF, v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog; Me, methyl; MEL18/PCGF2, polycomb group RING finger protein 2; Menin, multiple endocrine neoplasia I; miRNAs, microRNAs; MKRN3, makorin ring finger protein 3; MLL, myeloid/lymphoid or mixed-lineage leukemia; NAD+, nicotinamide adenine dinucleotide; NCOA6, nuclear receptor coactivator 6; ncRNAs, noncoding RNAs; NELL2, NEL-like 2; NRG1, neuregulin 1; OCT2/POU2F2, POU class 2 homeobox 2; OGA, O-GlcNAcase; O-GlcNAc, β-D-N-acetylglucosamine; OGT, N-acetylglucosamine transferase; p53/TP53, tumor suppressor protein p53; PA1/PAGR1, PAXIP1 associated glutamate-rich protein 1; PcG, polycomb group; PCGFs, polycomb group RING finger proteins; PER, period circadian clock; piRNAs, piwiRNAs; PHC, polyhomeotic-like protein; PMN, pre mammillary nucleus; POA, preoptic area; Pol II, RNA polymerase II; PRC, polycomb repressive complex; PTIP/PAXIP1, PAX interacting (with transcription-activation domain) protein 1; PTMs, posttranslational modifications; RBBP4, 5, 7, retinoblastoma binding proteins 4, 5 and 7; RFRP, RFamide-related peptide; RING1/2, really interesting new gene finger domain protein 1 or 2; RISC, RNA induced silencing complex; RPTPβ, Receptor-like Protein Tyrosine Phosphatase-β; RYBP, RING1 and YY1-binding protein; SCN, suprachiasmatic nucleus; SET1A/B, Su (var), enhancer of zeste, and trithorax] domain-containing A or B; SIRT1, Sirtuin 1; SNP, single nucleotide polymorphism; sRNAs, small RNAs; SUZ12, suppressor of ZESTE12; SynCAM1/TSLC1, Synaptic Cell Adhesion Molecule 1/Tumor Supressor of Lung Cancer1; TAC3/NKB, Tachykinin 3/Neurokinin B; TAC3R, Tachykinin 3 receptor; TET, Tet eleven translocation methylcytosine dioxygenase; TFs, transcription factors; TRGs, tumor related genes; Trx, trithorax; TrxG, trithorax group; TTF1/Nkx2.1, thyroid transcription factor 1/NK2 homeobox 1; Ub, ubiquitin; UDP-GlcNAc, uridine diphosphate N-Acetylglucosamine; USF2, upstream transcription factor 2; UTX/KDM6A, ubiquitously transcribed x chromosome tetratricopeptide repeat protein/lysine (K)-specific demethylase 6A; WDR5, WD (tryptophan-aspartic acid) repeat domain; WDR82, WD (tryptophan-aspartic acid) repeat domain 82; YAF2, YY1-associated factor 2; YY1, YIN-YANG-1; ZNF, zinc finger protein.

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1. Introduction

It is well-established that the initiation of mammalian puberty requires an increased secretory activity of a handful of hypothalamic neurosecretory neurons that produce the decapeptide gonadotropin-releasing hormone (GnRH). Because GnRH neurons are able to produce and release GnRH long before puberty, it is also clear that they are neither the ultimate responsible for the initiation of puberty nor constitute – under normal conditions – a significant obstacle for the pubertal process to be initiated earlier [reviewed in Ojeda and Skinner (2006)]. Instead, the secretory activity of GnRH neurons depends on trans-synaptic and glial inputs provided by different neurotransmitters, neuromodulators and cell–cell signaling molecules, derived from either neuronal subsets or glial cells functionally connected to GnRH neurons [reviewed in Ojeda and Skinner (2006), Terasawa and Fernandez (2001), Plant and Witchel (2006)]. While the trans-synaptic input can be either excitatory or inhibitory, the glial input is almost invariably excitatory (Prevot, 2002).

The unquestionable complexity of the cellular systems regulating GnRH neuron activity poses two important questions: what is the impact that genes expressed in such diverse cell populations may have on the initiation of puberty, and what are the mechanisms providing dynamic coordination to genetic networks that – operating within this diversity of cellular phenotypes – contribute to the central control of the pubertal process. The availability of new tools to explore the human genome has facilitated the identification of several genes that are essential for puberty to take place. They include *GNRHR*, which is necessary for pituitary gonadotrophs to respond to GnRH because it encodes the GnRH receptor (Bedecarrats and Kaiser, 2007), *LEP*, the gene encoding leptin, a cytokinine produced by adipocytes (Strobel et al., 1998) that is essential not only for the regulation of energy homeostasis, but also for the initiation of puberty (Ahima et al., 2000; Elias, 2012), and *LEPR* (encoding the leptin receptor) (Clement et al., 1998). Mutations affecting genes that have a primary role in regulating hypothalamic GnRH release include mutations in *KISS1R* (encoding the kisspeptin receptor) (Seminara et al., 2003; de Roux et al., 2003), *KiSS1* (encoding kisspeptins) (Lapatto et al., 2007; Topaloglu et al., 2012), *TAC3* (encoding neurokinin B, NKB), and *TAC3R* (encoding the NKB receptor) (Topaloglu et al., 2008). Others genes are required for GnRH neuron migration [reviewed in Sykiotis et al. (2010)]. More recently, two mutations causing premature puberty, instead of pubertal failure, have been described. One of these mutations results in the constitutive activation of *KISS1R* (Teles et al., 2008); the other appears to involve loss of an inhibitory input, because it involves inactivating mutations of *MKRN3*, which encodes a protein likely involved in the inhibitory control of puberty (Abreu et al., 2013). Despite the importance of this information, the fact that known gene mutations affecting puberty account for only a small percentage (less than 2%) of individuals with pubertal disorders, and the demonstration that sequence variations in more than 40 genes are associated with an early age at menarche (Ong et al., 2009; Perry et al., 2009; Sulem et al., 2009; He et al., 2009; Elks et al., 2010; Cousminer et al., 2013; Tanikawa et al., 2013), suggest that puberty is not an event triggered by a single gene. Instead, it appears to involve a diversity of genes, which – based on studies in animal models – have been postulated to be organized into functionally modules wired into larger gene networks (Lomniczi et al., 2013; Ojeda et al., 2006).

Even if the notion of many genes contributing to the pubertal process is accepted at face value, gene diversity does not explain how inherited, permanent changes in DNA sequence can regulate gene expression dynamically, while also imposing an encompassing level of coordination and transcriptional plasticity to gene sets controlling female reproductive development. In this article we will develop the concept that a biological regulatory system able to perform these functions is epigenetics – i.e., those heritable changes in gene expression that occur without changing the primary nucleotide sequence of a gene (Wolffe and Matzke, 1999; Herman and Baylin, 2003). Epigenetic mechanisms can not only provide gene-specific gatekeeper functions (Garcia-Bassets et al., 2007), but are also endowed with an unsuspected degree of plasticity able to transiently change gene expression within hours (Miller and Sweatt, 2007), and even minutes (Kangaspeska et al., 2008; Metivier et al., 2008). It is now clear that epigenetic information is also essential for a variety of neural functions, including memory formation (Miller and Sweatt, 2007), recovery of learning and memory (Fischer et al., 2007), dendritic development (Wu et al., 2007), neuronal and behavioral plasticity (Kumar et al., 2005), estrogen-induced gene expression (Perillo et al., 2008; Subramanian et al., 2008), glial–neuronal interactions (Shen et al., 2008), circadian rhythms (Nakahata et al., 2008; Bellet and Sassone-Corsi, 2010), and sexual differentiation of the brain (McCarthy et al., 2009; Semaan et al., 2012).

2. Neuronal circuits controlling LH release at puberty

As indicated earlier, the transysnaptic control of GnRH neurons is dual, that is, effected by counteracting excitatory and inhibitory inputs. A substantial fraction of the excitatory transsynaptic input to GnRH neurons is provided by glutamatergic neurons (Ojeda and Skinner, 2006; Plant and Witchel, 2006), but a more powerful – and anatomically discrete – neuronal system stimulating GnRH release is provided by hypothalamic neurons that secrete a set of four biologically active peptides known as kisspeptins (Oakley et al., 2009; d'Anglemont et al., 2010). These peptides result from proteolytic processing of a kisspeptin precursor that is the product of the *KISS1*/*Kiss1* gene (Ohtaki et al., 2001; Kotani et al., 2001). All kisspeptins are potent stimulators of GnRH release (Oakley et al., 2009; Shahab et al., 2005). The critical importance of these peptides for puberty was demonstrated 10 years ago by studies in humans showing that loss of function of *GPR54*/*KISS1R*, the gene encoding the kisspeptin receptor, results in pubertal failure (Seminara et al., 2003; de Roux et al., 2003).

Opposing this excitatory influence, there are three main neuronal subsets providing inhibitory transsynaptic regulation to GnRH neurons (Fig. 1): opiatergic [reviewed in Terasawa and Fernandez (2001)], RFamide-related peptide (RFRP)-containing neurons (Tsutsui et al., 2010), and GABAergic neurons (Terasawa and Fernandez, 2001; Herbison and Moenter, 2011).

Opiatergic neurons inhibit GnRH neuronal activity by releasing different peptides that bind to specific cell membrane receptors (Kordon et al., 1994) located both on GnRH neurons (Dudas and Merchenthaler, 2006) and on neurons controlling GnRH secretion (Ojeda and Skinner, 2006; Terasawa and Fernandez, 2001). A prominent example of this latter type of interaction is found in the ARC. In this region of the hypothalamus, kisspeptin neurons produce the opioid peptide dynorphin, which inhibits GnRH secretion at least in part by repressing kisspeptin release via a paracrine/autocrine type of interaction (Navarro et al., 2009).

RFRP is the mammalian ortholog of the peptide gonadotropin-inhibiting hormone (GnIH), first described in birds (Ebling and Luckman, 2008). RFRP neurons use the peptides RFRP1 and RFRP3 for transsynaptic communication. Both peptides are recognized by a high-affinity receptor termed GPR147 or NPFFR1 (Tsutsui et al., 2010; Hinuma et al., 2000), and a low-affinity receptor termed GPR74 or NPFFR2 (Fukusumi et al., 2006). GPR147 is expressed in GnRH neurons (Ducret et al., 2009; Poling et al.,

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