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Review

Regulation of mammary epithelial cell homeostasis by lncRNAs☆

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ABSTRACT

The epithelial cells of the mammary gland develop primarily after birth and undergo surges of hormonally regulated proliferation, differentiation, and apoptosis during both puberty and pregnancy. Thus, the mammary gland is a useful model to study fundamental processes of development and adult tissue homeostasis, such as stem and progenitor cell regulation, cell fate commitment, and differentiation. Long noncoding RNAs (lncRNAs) are emerging as prominent regulators of these essential processes, as their extraordinary versatility allows them to modulate gene expression via diverse mechanisms at both transcriptional and post-transcriptional levels. Not surprisingly, lncRNAs are also aberrantly expressed in cancer and promote tumorigenesis by disrupting vital cellular functions, such as cell cycle, survival, and migration. In this review, we first broadly summarize the functions of lncRNAs in mammalian development and cancer. Then we focus on what is currently known about the role of lncRNAs in mammary gland development and breast cancer.

This article is part of a Directed Issue entitled: The Non-coding RNA Revolution.

Contents

Abbreviations: lncRNA, long/large noncoding RNA; *Xist*, X-inactive specific transcript; mESC, mouse embryonic stem cell; *Evf2*, embryonic ventral forebrain 2; *Six3os*, sine oculis-related homeobox 3 homolog, opposite strand; *Dlx1as*, distal-less homeobox 1, antisense; *EGO*, eosinophil granule ontogeny; *HOTAIRM1*, HOX antisense intergenic RNA myeloid 1; *LincRNA-EPS*, lincRNA erythroid prosurvival 1; *Lnc-MD1*, long noncoding RNA, muscle differentiation 1; *ANCR*, anti-differentiation noncoding RNA; *TINCR*, terminal differentiation-induced ncRNA; *Bvht*, braveheart; *Fendrr*, Fetal-lethal noncoding developmental regulatory RNA; SCNA, somatic copy number alteration; *PRNCR1*, prostate cancer noncoding RNA 1; *PCGEM1*, prostate cancer gene expression marker 1; *PANDA*, p21 associated ncRNA DNA damage activated; NF-YA, nuclear transcription factor Y, alpha; *MALAT1*, metastasis associated lung adenocarcinoma transcript 1; *BC200*, brain cytoplasmic RNA 200; miRNA, microRNA; piRNA, PIWI-interacting RNA; snoRNA, small nucleolar RNA; eRNA, enhancer RNA; PRC2, polycomb repressive complex 2; LSD1, lysine-specific demethylase 1; REST, repressor element-1 (RE1) silencing transcription factor; CoREST, co-repressor for REST; PRC1, polycomb repressive complex 1; MLL1, mixed lineage leukemia 1; TEB, terminal end bud; *SRA*, steroid receptor RNA activator; *mPINC*, mouse pregnancy induced noncoding RNA; *Zfas1*, Znfx1 antisense RNA 1; *Znfx1*, zinc finger, NFX1-type containing 1; *RbAp46*, retinoblastoma associated protein 46; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; GRO-seq, global run-on sequencing; *MEG3*, maternally expressed gene 3; *PTENP1*, phosphatase and tensin homolog pseudogene 1; PTEN, phosphatase and tensin homolog; MRE, microRNA recognition element; asRNA, antisense RNA; *GAS5*, growth arrest-specific transcript 5; GR, glucocorticoid receptor; AR, androgen receptor; *UCA1*, urothelial carcinoma-associated 1; hnRNP I, heterogeneous nuclear ribonucleoprotein I; ATM, ataxia-telangiectasia mutated; *LSINCT5*, long stress-induced noncoding transcript 5; *NEAT1 and 2*, nuclear enriched abundant transcript 1 and 2; PSPC1, paraspeckle component 1; BRCA1, breast cancer 1, early onset; DDR, DNA damage response; H4, histone 4; HG, high grade; NHG, non-high grade; *treRNA*, translational regulatory RNA; EMT, epithelial-to-mesenchymal transition; SRSF1, 2 and 3, serine/arginine-rich splicing factor 1, 2 and 3; Pc2, polycomb 2 homolog; *HOTAIR*, HOX antisense intergenic RNA; EZH2, enhancer of zeste homolog 2; *PCDH*, protocadherin; *EPHA1*, ephrin type-A receptor 1; *IGF2*, insulin-like growth factor 2; IGN, imprinted gene network; *Igfr1*, insulin-like growth factor type 1 receptor; *RB1*, retinoblastoma 1; NR, nuclear receptors; MMTV LTR, mouse mammary tumor virus long terminal repeat; *PCA3*, prostate cancer gene 3.

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1. Introduction

1.1. LncRNAs and development

A fundamental goal in developmental biology is to understand how stem and progenitor cells differentiate and perform specialized functions in each tissue type of a particular organism. Cells proceed toward differentiation through highly coordinated, stepwise changes in gene expression that are largely regulated by cell-type dependent transcription factor networks, resulting in a mixed population of stem, progenitor, and differentiated cell types. The precise regulation of this cellular hierarchy is essential for creating and maintaining the structure and function of an organ. Additionally, the preservation of each cell type in a given tissue requires maintenance of their unique patterns of gene expression, which is thought to be regulated predominantly by epigenetic mechanisms. In the past decade, long noncoding RNAs (lncRNAs) have emerged as significant regulators of tissue- and cell-specific gene expression by diverse mechanisms, many of which result in targeted epigenetic modifications. Therefore, it is not surprising that there is growing evidence of an instructional role for lncRNAs in mediating key processes in cellular differentiation and development (Hu et al., 2011).

Relatively few lncRNAs have identified functions. However, a large portion of these regulate developmental processes in embryonic and adult mammalian tissue. Some of the earliest characterized lncRNAs regulate distinct epigenetic processes that are critical for embryonic development, such as the regulation of genomic imprinting by *H19* (Bartolomei and Ferguson-Smith, 2011) and X-inactivation by *Xist* (Jeon et al., 2012). Imprinting and X-inactivation are both mediated by multiple lncRNA-chromatin modifying complexes that target and silence genes in *cis* (Lee and Bartolomei, 2013). In addition, large-scale analyses using mouse embryonic stem cells (mESCs) have identified hundreds of lncRNAs, some of which are differentially expressed in various stages of mESC differentiation (Dinger et al., 2008; Guttman et al., 2009). Loss-of-function studies of dozens of mESC lncRNAs show that they act to repress lineage commitment programs to maintain the mESC pluripotent state (Guttman et al., 2011). Other lncRNAs, such as *Mira*, may be induced by, and necessary for, mESC differentiation (Bertani et al., 2011). Taken together, these data support a central role for lncRNAs in regulating key processes during embryogenesis, including genomic imprinting and dosage compensation, as well as mESC pluripotency and differentiation.

In the adult, lncRNAs often show precise spatiotemporal expression patterns (Cabili et al., 2011; Derrien et al., 2012; Djebali et al., 2012; Ravasi et al., 2006), reflecting their potential role in regulating lineage commitment and differentiation. Consistent with this proposal, several lncRNAs have been shown to regulate cell fate decisions across a broad range of tissues. For example, global analyses have identified a large number of lncRNAs that show discrete patterns of expression in the central nervous system (Mercer et al., 2008; Ng et al., 2012; Ponjavic et al., 2009; Qureshi et al., 2010). Further studies have shown that several lncRNAs are required for proper neural differentiation and development, such as *Evf2* (Bond et al., 2009), *Six3os*, and *Dlx1as* (Ramos et al., 2013). In addition, the expression of several lncRNAs is induced during, and necessary for, the differentiation of distinct hematopoietic lineages, including *EGO* (Wagner et al., 2007), *HOTAIRM1* (Zhang et al., 2009), and *LincRNA-EPS* (Hu, Yuan, 2011). Another lncRNA called *Linc-MD1* promotes muscle differentiation by binding and sequestering miRNAs that repress myogenic genes (Cesana et al., 2011). In the epidermis, *ANCR* represses terminal differentiation by an unknown mechanism (Kretz et al., 2012), whereas *TINCR* promotes terminal differentiation by binding and stabilizing differentiation mRNAs (Kretz et al., 2013). LncRNAs have also been shown to regulate heart development, likely via epigenetic mechanisms. The lncRNA *Bvht* interacts with the PRC2 complex and is required for cardiomyocyte differentiation *in vitro* (Klattenhoff et al., 2013), whereas the lncRNA *Fendrr* binds to both the PRC2 and MLL complexes, and it is essential for proper mouse heart development *in vivo* (Grote et al., 2013). Interestingly, recent evidence shows that several imprinted genes, including the lncRNA *H19*, are not only expressed embryonically, but are also enriched specifically in adult somatic stem cells where they may play an additional role in regulating the balance between stem cell self-renewal and differentiation in several adult tissues (Berg et al., 2011; Ferron et al., 2011; Venkatraman et al., 2013; Zacharek et al., 2011).

1.2. LncRNAs and cancer

Since lncRNAs regulate critical pathways in tissue development and maintenance, it might be assumed that the misregulation of lncRNAs could disrupt these delicate processes and lead to tumorigenesis. Recent transcriptional profiling of multiple human tissues, including both normal and tumor samples, have indeed begun to provide global evidence for the misexpression of lncRNAs in cancer (Brunner et al., 2012; Gibb et al., 2011b). These studies have validated the tissue-specific expression of lncRNAs in normal tissues, and have identified large sets of lncRNAs that are aberrantly expressed in either a specific cancer or multiple types of cancer. A recent large-scale study went a step further by integrating microarray data of lncRNA expression from 1,300 tumors, spanning four types of cancer, with clinical outcome and somatic copy number alterations (SCNAs) data, and identified 80–300 potential lncRNA drivers of cancer progression in each of the four cancer types (Du

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