Long non-coding RNAs in rabbit physiology and development

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Abstract. Long non-coding RNAs (lncRNAs) have emerged as key regulators of gene expression across diverse biological systems, including in the rabbit (*Oryctolagus cuniculus*), an increasingly relevant model for developmental, physiological and biomedical research. This mini-review synthesizes current knowledge on lncRNA characteristics, regulatory mechanisms and functional roles in rabbit physiology and development. We highlight evidence from transcriptomic studies describing dynamic and tissue-specific lncRNA expression patterns during pre-implantation and post-implantation embryogenesis, as well as in postnatal adipose tissue and skeletal muscle. Particular emphasis is placed on post-transcriptional regulatory mechanisms, including modulation of mRNA stability, translation and interaction with miRNAs and RNA-binding proteins. The involvement of lncRNAs in key developmental signaling pathways, such as Wnt, PI3K–Akt and AMPK, is discussed, alongside their emerging roles in metabolic regulation and embryonic morphogenesis. In addition, insights from mammalian models are integrated to propose mechanistic frameworks for lncRNA-mediated stress responses in rabbits, including heat, cold and oxidative stress. Collectively, the available evidence supports a central role for lncRNAs as dynamic regulators of gene expression networks underlying rabbit development, metabolism and stress adaptation, while also highlighting current knowledge gaps and future research directions.
Keywords: long non-coding RNAs, rabbit, Oryctolagus cuniculus, gene regulation, embryonic development, post-transcriptional regulation, transcriptomics, adipose tissue, skeletal muscle, stress response, epitranscriptomics.

Introduction. Long non-coding RNAs (lncRNAs) are emerging as key regulators of gene expression in mammals, including the rabbit, a relevant model for growth, metabolism and development. Rabbit specific transcriptomic studies now profile lncRNAs in embryos, adipose tissue and skeletal muscle, while broader mammalian work clarifies general mechanisms of lncRNA action in transcriptional and post transcriptional regulation, development and stress responses (Shi et al., 2021; Wang et al., 2018; Kuang et al., 2019; Statello et al., 2020; Fernandes et al., 2019; Mattick et al., 2023; Sarropoulos et al., 2019; Zhu et al., 2022; Oo et al., 2021; Darbellay & Necsulea, 2019).

The aim of this mini-review is to provide an updated and integrative overview of long non-coding RNAs in rabbit physiology and development, with a particular focus on their regulatory mechanisms and functional significance. Specifically, this review seeks to: (i) summarize the general molecular features and modes of action of lncRNAs; (ii) compile and synthesize rabbit-specific transcriptomic evidence across developmental stages and tissues; (iii) evaluate the role of lncRNAs in post-transcriptional regulation and key biological pathways; and (iv) contextualize rabbit findings within broader mammalian frameworks, particularly in relation to stress response mechanisms. Through this approach, the review aims to identify emerging patterns, highlight current limitations and outline future directions for lncRNA research in this species.

General Features and Mechanisms of lncRNAs. LncRNAs are >200 nt transcripts, often shorter, with fewer exons and lower expression than mRNAs, and typically show strong tissue and stage specific expression (Wang et al., 2018; Kuang et al., 2019;

Statello et al., 2020; Fernandes et al., 2019; Mattick et al., 2023; Oo et al., 2021; Darbellay & Necsulea, 2019). They regulate gene expression at multiple levels: chromatin modification and transcriptional control in cis and trans; modulation of nuclear bodies and enhancer activity; and control of mRNA stability, splicing and translation in the cytoplasm (Kuang et al., 2019; Statello et al., 2020; Fernandes et al., 2019; Mattick et al., 2023; Ferrer & Dimitrova, 2024; Oo et al., 2021). Many lncRNAs act as molecular scaffolds or guides for RNA binding proteins and chromatin complexes, or as decoys/competitors for RNA and protein partners, thereby shaping developmental and stress response programs (Kuang et al., 2019; Statello et al., 2020; Fernandes et al., 2019; Mattick et al., 2023; Ferrer & Dimitrova, 2024; Oo et al., 2021; Wang et al., 2019). Comparative and consensus analyses indicate that while many lncRNAs are species specific and weakly constrained, a subset expressed in developing organs shows higher promoter conservation and clear functional signatures (Mattick et al., 2023; Sarropoulos et al., 2019; Oo et al., 2021; Darbellay & Necsulea, 2019).

Rabbit lncRNAs: Developmental and Tissue Context. A cross species developmental atlas identified ~15,000–35,000 candidate lncRNAs per species, including rabbit, with dynamic and often organ specific expression across brain, kidney, liver, testes and other organs from early organogenesis to adulthood (Sarropoulos et al., 2019). During development, lncRNA repertoires shift from more broadly expressed, conserved transcripts towards increasingly lineage and organ specific lncRNAs, consistent with specialized roles in organ maturation (Mattick et al., 2023; Sarropoulos et al., 2019; Oo et al., 2021; Darbellay & Necsulea, 2019). In rabbits, dedicated studies now describe lncRNA landscapes in pre implantation embryos, later embryogenesis, adipose tissue and skeletal muscle, providing an entry point to functional interpretation in physiology (Shi et al., 2021; Wang et al., 2018; Ji et al., 2021; Scholda et al., 2023; Sarropoulos et al., 2019; Zhu et al., 2022) (Table 1).

Table 1

Rabbit lncRNA resources across organs and stages

Rabbit system / stage	*Main lncRNA findings*	*References*
Pre-implantation oocyte–morula	2,673 known lncRNAs; stage-specific, dynamic expression; maternal clearance and zygotic activation waves; candidates linked to transcription/translation control and mRNA surveillance	(Shi et al., 2021)
Post-implantation embryo morphogenesis	719 lncRNAs differentially expressed (S1–S3); network implicates lncRNAs with WNT3, TBX1, FGFR2 in Wnt, PI3K–Akt, Ca^{2+} signaling	(Ji et al., 2021; Scholda et al., 2023)
Postnatal visceral adipose tissue	Hundreds of differentially expressed lncRNAs across 35–85–120 d; targets enriched in oxidative phosphorylation and metabolic pathways	(Wang et al., 2018)
Skeletal muscle (fetal to adult)	554, 19, 429 DE lncRNAs across fetal, post-weaning, adult stages; key lncRNAs co-expressed with PI3K–Akt, AMPK, mTOR pathway genes	(Zhu et al., 2022)
Cross-organ developmental atlas (incl. rabbit)	Thousands of lncRNAs per organ; embryonic/somatic lncRNAs more conserved and functionally constrained	(Sarropoulos et al., 2019; Darbellay & Necsulea, 2019).

Post transcriptional Regulation in Rabbit Physiology. General lncRNA biology shows extensive roles in post transcriptional control, including splicing modulation, mRNA stability/decay, miRNA sponging, translation control and post translational modifications (Kuang et al., 2019; Statello et al., 2020; Fernandes et al., 2019; Mattick et al., 2023; Oo et al., 2021; Wang et al., 2019). In rabbits, embryo and tissue specific datasets suggest analogous mechanisms, mainly inferred via co expression and target prediction.

In pre implantation development, RNA seq profiling of mature oocyte, 2, 4, 8 cell and morula stages identified 2,673 known lncRNAs with strongly dynamic expression (Shi et al., 2021). Differentially expressed lncRNAs between oocyte and 2 cell, and between 8

cell and morula, coincide with minor and major zygotic genome activation, respectively, and predicted targets are enriched in intracellular metabolism, organelle organization and signaling, but also in processes directly related to transcription and translation (Shi et al., 2021). Functional analyses indicate that late degraded maternal lncRNAs may participate in mRNA degradation via the mRNA surveillance pathway, suggesting a direct contribution to post transcriptional clearance of maternal transcripts (Shi et al., 2021). Correlation analyses highlight specific lncRNAs (ENSOCUG00000034943, ENSOCUG00000036338) as regulators of late pre implantation development, likely through control of gene expression networks that include mRNA processing and turnover (Shi et al., 2021).

In postnatal visceral adipose tissue, 30–107 lncRNAs are differentially expressed across 35, 85 and 120 d, with cis and trans target prediction implicating 72 and 20 protein coding genes, respectively (Wang et al., 2018). GO and KEGG analyses show enrichment in oxidative phosphorylation, glyoxylate and dicarboxylate metabolism and other adipose growth-related pathways, indicating that lncRNAs influence metabolic gene expression and potentially mitochondrial function at post transcriptional and translational levels (Wang et al., 2018).

Rabbit skeletal muscle development also reveals stage specific lncRNAs linked to energy and growth pathways. Co expression networks suggest that LINC 2903, LINC 2374 and LINC 8591 participate in early maintenance of skeletal muscle development via AMPK and PI3K–Akt signaling, while LINC 5617 may support embryonic myoblast proliferation, and LINC 8613 and LINC 8705 may help provide energy postnatally, likely through regulation of metabolic and anabolic genes (Zhu et al., 2022). These patterns align with broader evidence that lncRNAs coordinate mRNA stability and translation in metabolic and signaling pathways (Kuang et al., 2019; Fernandes et al., 2019; Mattick et al., 2023; Oo et al., 2021).

LncRNAs in Rabbit Embryonic Development. LncRNAs are particularly enriched in developmental contexts across mammals, with many functionally constrained loci expressed in embryonic organs (Mattick et al., 2023; Sarropoulos et al., 2019; Oo et al., 2021; Darbellay & Necsulea, 2019). In rabbits, several high-resolution transcriptomic studies place lncRNAs at the core of embryogenesis.

During pre-implantation development, dynamic lncRNA expression accompanies the maternal to zygotic transition. Between the oocyte and 2 cell stages, 107 lncRNAs are differentially expressed; between 8 cell and morula, 419 lncRNAs change, mirroring minor and major zygotic genome activation waves (Shi et al., 2021). Target prediction and pathway analysis indicate that stage specific lncRNAs promote embryo cleavage and synchronized development by regulating gene transcription/translation, intracellular metabolism, organelle biogenesis and intercellular signaling (Shi et al., 2021). Sequential degradation of maternal lncRNAs via maternal and zygotic pathways further underscores their programmed roles in resetting the transcriptome, including potential participation in mRNA surveillance and degradation pathways essential for developmental progression (Shi et al., 2021).

Whole transcriptome sequencing at later embryonic stages (S1–S3) identifies 719 differentially expressed lncRNAs, of which 241 are significantly associated with morphogenesis and development (Ji et al., 2021; Scholda et al., 2023). Network analysis links specific lncRNAs (e.g. TCONS_00009253, TCONS_00010436) and circRNAs with co expressed morphogenetic regulators TBX1, WNT3 and FGFR2, which are persistently downregulated as corresponding non coding RNAs show staged expression changes (Ji et al., 2021; Scholda et al., 2023). Enrichment in Wnt, PI3K–Akt and calcium signaling pathways suggests that rabbit embryonic lncRNAs modulate canonical developmental signaling cascades at both transcriptional and post transcriptional levels (Ji et al., 2021; Scholda et al., 2023).

Cross species developmental analyses reinforce this picture: lncRNAs with dynamic, conserved expression patterns are enriched during organogenesis, with a transition from broadly expressed early developmental lncRNAs to more organ and lineage specific ones later, indicating successive layers of regulatory refinement (Mattick et al., 2023;

Sarropoulos et al., 2019; Oo et al., 2021; Darbellay & Necsulea, 2019). Functionally constrained lncRNA loci in developing organs often show higher promoter conservation than their exonic sequences, implying that transcription at these loci, and not only the RNA product, contributes to developmental gene regulation (Mattick et al., 2023; Sarropoulos et al., 2019; Darbellay & Necsulea, 2019).

LncRNAs and Stress Responses: Implications for Rabbit Physiology. Dedicated lncRNA–stress studies in rabbit are not yet available in the provided corpus, but mammalian and cellular models offer mechanistic frameworks likely applicable to rabbits. Across species, lncRNAs are central regulators of cellular stress responses, integrating diverse inputs (heat, cold, oxidative, metabolic and immune stress) and influencing decisions between adaptation and cell death (Statello et al., 2020; Dou et al., 2021; Mattick et al., 2023; Ferrer & Dimitrova, 2024; Oo et al., 2021; Wang et al., 2019; Meng et al., 2020).

In mammalian cells, several lncRNAs regulate heat shock responses. A heat inducible nuclear lncRNA in mouse cells, termed Heat, is robustly upregulated upon heat shock and functions as a HSF1 directed transcriptional brake: it binds heat shock factor 1, targets stress genes in trans, and via extensive m⁶A modification and interaction with the nuclear m⁶A reader YTHDC1, forms a transcriptional silencing complex that attenuates stress gene expression and terminates the heat shock response (Ji et al., 2021). Depletion of m⁶A on Heat results in prolonged stress gene activation, illustrating how lncRNA epitranscriptomic modification fine tunes stress transcription (Ji et al., 2021).

Genome wide analyses in heat stressed rats further demonstrate that hundreds of liver and adrenal lncRNAs are differentially expressed after acute heat exposure; their predicted targets are enriched in insulin, glucagon, and cell cycle pathways, as well as heat shock protein (HSP) genes such as Hsf4, Hsph1, Hspb1 and Dnaj family members (Dou et al., 2021). These lncRNAs likely shape endocrine and chaperone responses necessary for systemic adaptation to thermal stress (Statello et al., 2020; Dou et al., 2021). In cold stressed rat liver, 273 differentially expressed lncRNAs are identified; functional predictions and co expression networks highlight a key lncRNA (MSTRG.80946.2) that regulates genes involved in fatty acid metabolism, PI3K–Akt signaling and immune and metabolic adaptation to cold (Ji et al., 2020). These findings point to a recurrent role for stress responsive lncRNAs in energy metabolism, endocrine signaling and immune modulation under temperature stress (Statello et al., 2020; Dou et al., 2021; Ji et al., 2020; Wang et al., 2019).

Oxidative stress provides another well-defined axis (Petrescu-Mag & Gavriloaie, 2025). Multiple lncRNAs regulate redox balance, either promoting antioxidant defenses or exacerbating oxidative damage, with implications for cardiovascular and neurodegenerative disease (Wang et al., 2019; Meng et al., 2020). For example, the lncRNA Hotair is upregulated in myocardial ischemia–reperfusion; its overexpression activates AMPK via an EZH2/miR 451/Cab39 axis and thereby suppresses oxidative stress and cardiomyocyte apoptosis, whereas knockdown exacerbates injury (Meng et al., 2020). More broadly, lncRNAs can influence ROS production, antioxidant enzyme expression and downstream apoptotic pathways, functioning as potential biomarkers and regulators in oxidative stress related pathologies (Wang et al., 2019; Meng et al., 2020).

At a systems level, stress related lncRNAs operate through canonical lncRNA mechanisms: guiding chromatin complexes to stress responsive loci; scaffolding transcriptional or repressor complexes; modulating the stability and translation of stress related mRNAs; and reorganizing nuclear bodies and phase separated condensates under stress (Ji et al., 2021; Kuang et al., 2019; Statello et al., 2020; Mattick et al., 2023; Ferrer & Dimitrova, 2024; Oo et al., 2021; Wang et al., 2019). Given the presence of analogous heat, cold and oxidative stress pathways, as well as conserved components such as HSF1, HSPs, AMPK and PI3K–Akt signaling, these mechanistic paradigms established in rodents, humans and other species provide a conceptual framework for future work on lncRNA mediated stress responses in rabbits (Ji et al., 2021; Statello et al., 2020; Dou et al., 2021; Mattick et al., 2023; Ji et al., 2020; Oo et al., 2021; Wang et al., 2019; Meng et al., 2020) (Figure 1).

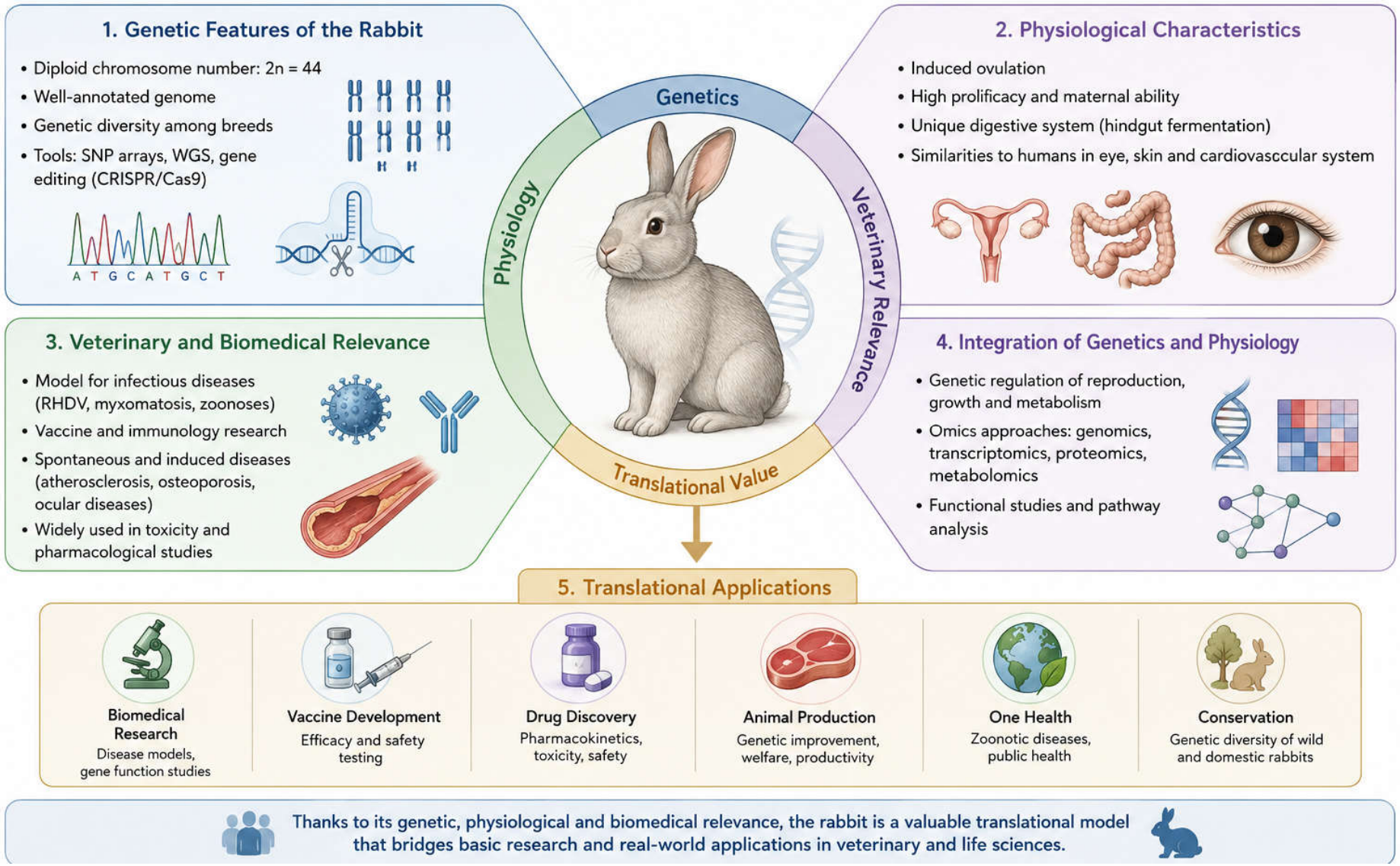

Figure 1. The rabbit as a translational model: bridging genetics, physiology and veterinary research.

Conclusions. Long non-coding RNAs represent a major regulatory layer in rabbit biology, characterized by dynamic, tissue-specific and developmentally regulated expression patterns. Current evidence indicates that lncRNAs are deeply integrated into gene regulatory networks controlling embryogenesis, tissue differentiation and metabolic processes, largely through post-transcriptional and epigenetic mechanisms. In particular, their involvement in key signaling pathways such as Wnt, PI3K–Akt and AMPK underscores their relevance in coordinating growth and physiological homeostasis.

Despite these advances, functional characterization of rabbit lncRNAs remains limited, with most insights derived from transcriptomic profiling and predictive analyses rather than direct experimental validation. Furthermore, the role of lncRNAs in stress responses in rabbits is still largely unexplored, although comparative data from other mammals suggest conserved regulatory frameworks involving chromatin modulation, RNA stability control and epitranscriptomic modifications.

Future research should prioritize functional studies, including loss- and gain-of-function approaches, integration of multi-omics datasets and investigation of lncRNA–protein and lncRNA–RNA interaction networks. Expanding research in these directions will not only clarify the biological significance of lncRNAs in rabbits but also strengthen the utility of this species as a translational model in developmental biology, physiology and biomedical sciences.

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