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ncRNAs REGULATION OF SALT AND DROUGHT RESISTANCE IN CAMELS

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ABSTRACT

Camels exhibit extraordinary resilience to arid environments by enduring extreme salinity and drought through specialised adaptations. Emerging research highlights the critical regulatory roles of non-coding RNAs (ncRNAs) in mediating salt and drought resistance. ncRNAs play a pivotal role by integrating osmoregulatory, metabolic and antioxidative responses to fortify camels against extreme desert condition. This review synthesises recent advances in our understanding of evolutionary adaptations and proposes strategies for improving stress tolerance in agriculturally significant species.

Key words: Camels, drought resistance, homeostasis, metabolic adaptation, ncRNAs

Camels breeding has a long history and has played a pivotal role in sustaining desert and semi-desert ecosystems. These animals have evolved numerous adaptive traits supporting resistance to heat, salinity and aridity environments (Rehan and Qureshi, 2006). As species long habituated to desert environments, camels exhibit stress -resistance mechanisms that enable survival under conditions of water scarcity and elevated temperatures. Comparative genomic studies across desert mammals reveal substantial functional overlap in gene classes and metabolic pathways, reflecting the phenotypic complexity required for adaptation to resource-limited and thermally extreme habitats (Rocha *et al,* 2021).

Non-coding RNA (ncRNA) is commonly employed for RNA transcript that does not encode proteins, high-throughput techniques have produced remarkable evidences for ncRNA-associated interactions in different kinds of cellular functions (Eddy, 2001). It indirectly controls a wide range of biological processes, including cellular metabolism, developmental programmes, transcriptional activity, post- transcriptional modifications, mRNA stability and translation and even protein degradation and translocation (Storz, 2002; Mattick *et al,* 2006). The post -transcriptional regulatory capacity of ncRNAs significantly impacts gene expression dynamics. Studies have demonstrated that miRNA can inhibit the expression of protein-coding genes by binding to 3′ untranslated regions (UTRs) and protein-coding regions of a targeted mRNA (Bartel, 2004). The ncRNA family encompasses multiple subtypes: small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), tRNA-derived small RNAs (tsRNAs) and others (Borsani *et al,* 2005; Girard *et al,* 2006; Ning and Li, 2018). Small interfering RNAs (siRNAs) constitute a class of 20-25 nucleotide double-stranded RNA molecules originating from perfectly complementary fold-back structures (Hamilton and Baulcombe, 1999). MicroRNAs (miRNAs), endogenous small ncRNAs of approximately 21-23 nucleotides, are processed from transcribed hairpin precursors (Lee *et al,* 1993; Lagos-Quintana *et al,* 2001). Piwi-interacting RNAs (piRNAs) derive their nomenclature from associated PIWI proteins, as these Argonaute family members mediate precursor piRNA processing through the Ping-Pong amplification cycle (Aravin *et al,* 2007; Siomi *et al,* 2011). Long non-coding RNAs (lncRNAs), defined as non-protein-coding transcripts exceeding 200 nucleotides, were initially identified in murine systems through early 1990s cDNA library analysis (Brannan *et al,* 1990). long ncRNAs were first described during the large-scale sequencing of full-length cDNA libraries in the mouse (Okazaki, 2002) (Table 1).

The first draft of both domestic (*Camelus bactrianus*) and wild Bactrian camel (*Camelus ferus*) genomes was reported in 2012. The size of Bactrian camel genome was reported as 2.38 Gb and contained 20,821 genes (BCFSAC, 2012). A similar report, related to sequencing the genome of Bactrian, dromedary and alpaca camels (*Vicugna pacos*), was published in 2014. The genome size of Bactrian camel reported

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in this study (2.45 Gb) was similar to the earlier reported. The non-coding RNA genes of Dromedary, Bactrian and alpaca genomes shared similar copy numbers. non-coding RNA genes showed remarkable consistency: 1,942 in Bactrian camels, 2,209 in dromedaries and 2,328 in alpacas (Wu *et al,* 2014).

Camels possess multiple physiological adaptations to survive harsh environments, including: water conservation mechanisms, highly efficient kidneys, specialised fat storage in humps, dehydration-resistant blood cells and metabolic flexibility. These adaptations are supported by specific genetic foundations: Water conservation primarily involves genes regulating renal function, particularly those associated with ion transport and urine concentration mechanisms. Additional genetic adaptations likely minimise water loss through reduced sweating and respiratory evaporation. Metabolic adaptations feature two key components: First, the preferential utilisation of fat stores (rather than carbohydrates) to generate metabolic water during prolonged fasting. Second, enhanced antioxidant systems combat oxidative stress induced by dehydration, which could otherwise cause cellular damage (Wu *et al,* 2014). Non-coding RNAs (ncRNAs) serve as master regulators in camels, enabling them to survive extreme aridity and salinity by coordinating salt tolerance and drought resistance through shared and distinct molecular pathways (Fig 1).

Osmoregulation and Ion Homeostasis

Under osmotic stress, ncRNAs modulate osmoregulation and ion homeostasis by targeting ion transport-related genes, such as sodium-potassium pumps and channels, thereby reducing cellular ion toxicity. Notably, sodium reabsorption and water balance in the kidney have been identified as an adaptation to desert environment (Wu *et al,* 2014; Okazaki *et al,* 2002) Hypertonicity serves as the physiological foundation for renal water balance and reabsorption, mediated through a gene network that coordinates water reabsorption with glucose-regulated osmoregulation and water conservation. Specifically, the expression of osmoregulation-associated genes in osmoregulation in the renal medulla (Wu *et al,* 2014).

Aquaporins (AQPs), a family of water channel proteins, play crucial roles in renal water handling and therefore in the regulation of body water homeostasis (Nielsen *et al,* 1999; Ingelfinger *et al,* 2015; Kortenoeven and Fenton, 2014). AQP1, AQP2 and AQP3 were the top three differentially expressed genes in the renal cortex and medulla under water-restricted conditions. This differential expression pattern may enable camels to enhance water reabsorption efficiency in water-scarce environments (Wu *et al,* 2014,). Notably, two AQP2-targeting miRNAs (miR-32 and miR-137) have been shown to downregulate AQP2 expression in kidney collecting duct cells through mechanisms independent of vasopressin regulation (Kim *et al,* 2015; Gomes *et al,* 2018).

The microRNA-30 (miR-30) family, an important subgroup of miRNAs, comprises five precursor members that generate six mature miRNA molecules: miR-30a, miR-30b, miR-30c-1, miR-30c-2, miR-30d and miR-30e. These molecules are encoded by six distinct genes located on human chromosomes 1, 6 and 8 (Mao *et al,* 2018). Research has demonstrated that miR-30 negatively regulates the uPAR-ITGB3 axis through the calcineurin-NFATC signaling pathway, revealing a novel mechanism underlying podocyte injury in glomerular diseases. This discovery elucidates the functional relationships among key molecular players governing podocyte pathophysiology (Lang *et al,* 2019).

lncRNAs play multifaceted roles in osmoregulation and stress adaptation through

Table 1. Classes of regulatory ncRNAs and their sizes and functions.

Name	Definition	Function	Size	Ref
lncRNA	long noncoding RNA	autonomously transcribed RNA that does not encode a protein; often capped and polyadenylated; can be nuclear, cytoplasmic or both	>200 nt	Brannan *et al,* 1990; Okazaki, 2002
miRNA	microRNA	RNA that in complex with AGO protein, uses seed sequences near its 50 end to base pair with a target mRNA to induce deadenylation and decay or translational regulation	22 nt	Lee *et al,* 1993
ncRNA	noncoding RNA	an RNA that does not encode a protein,but has other cellular functions	–	Eddy *et al,* 2001
piRNA	PIWI-associated RNA	RNA that directs the modification of chromatin to repress transcription; best characterised in the male germline	27 nt	Aravin *et al,* 2006; Girard *et al,* 2006

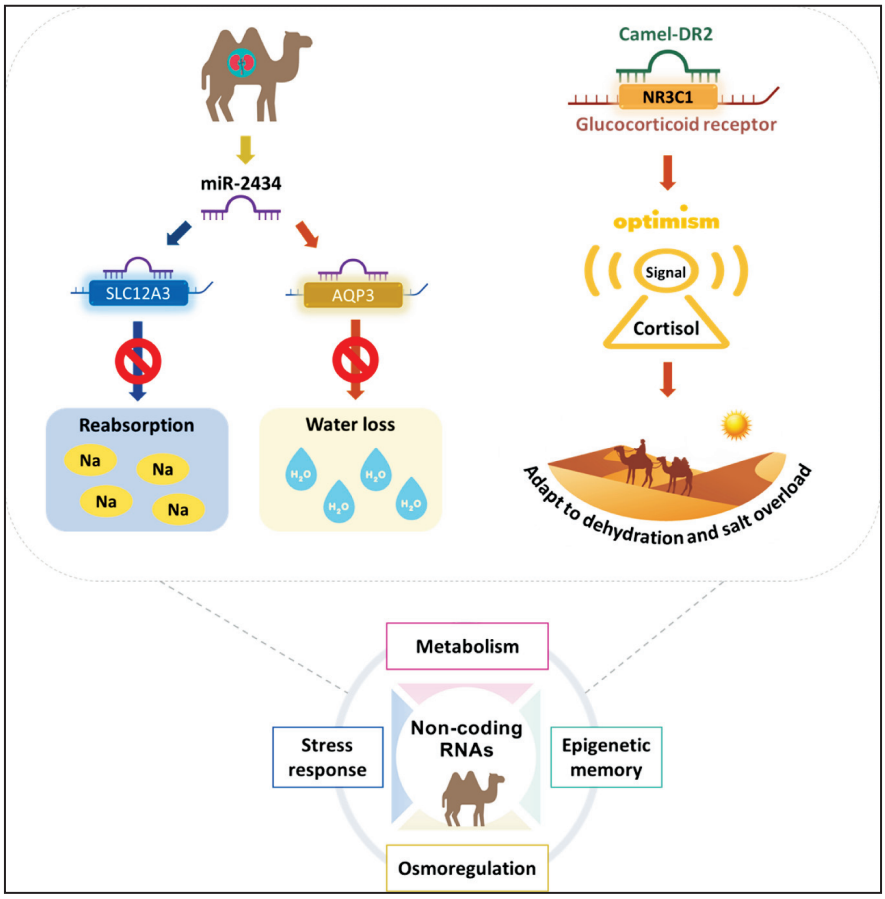

Fig 1. ncRNAs regulate salt and drought stress resistance in camels through various regulatory mechanisms.

diverse molecular mechanisms. Specifically, lncRNAs can serve as molecular scaffolds to stabilise key enzymes such as betaine-aldehyde dehydrogenase (BADH), a rate-limiting enzyme critical for betaine biosynthesis during osmotic stress. The camel-specific lncRNA DR1 exemplifies this regulatory capacity by coordinately modulating two essential pathways: 1) PPARγ-mediated lipid metabolism required for metabolic water generation and 2) SLC26A3-dependent intestinal ion transport (Makishima, 2005), This dual regulation establishes a crucial link between cellular energy production and salt-water homeostasis in dehydrated camels. Another evolutionarily conserved lncRNA, H19, demonstrates complementary protective functions (Wu and Huang, 2023). It stabilises BADH protein levels to maintain betaine synthesis while concurrently upregulating HSP70 expression, thereby preserving proteostasis under dehydration conditions. Furthermore, emerging evidence suggests (Makishima, 2005) that lncRNAs may orchestrate epigenetic responses to environmental challenges through recruitment of chromatin modifiers. This mechanism potentially maintains transcriptionally active chromatin states at stress-responsive loci, including those encoding heat shock proteins and drought tolerance factors.

lncRNAs could stabilise transcripts of urea transporters (e.g., UT-A1/2), enhancing urea recycling to concentrate urine without water loss. Post-transcriptional regulation of ncRNAs in renal cortex, For camel renal cortex under salt stress and water deprivation stress, the diferentially expressed lncRNA.Salt resistance-related genes with significantly different expression were involved in 13 genes, four novel significantly down-regulated lncRNAs (LNC002600, LNC000062, LNC001899 and LNC000331) were detected under salt stress, four novel salt-resistance-related lncRNAs in renal cortex and proposed the ncRNAs-related post-transcriptional regulation pathway to explain how camels respond to salt stress and water-deprivation stress(Cao *et al*, 2019). The response pathway of post-transcriptional regulation concerning salt and water-deprivation stresses was put forward, involving preventing sodium from entering the cell, purifying of water and compensating neutral amino acids by

miR-193b, miR-542-5p interaction with SLC6A19 mRNA.

Under water-deprivation stress, by RNA-sequencing of camel renal medulla associated with regulating water metabolism, 575 significantly differential alternative splicing events (ASEs) along with 17 mRNAs, 26 miRNAs and no lncRNA were detected (Zhang *et al,* 2020). Among these, The down-regulated ACLY and LOC105061856, along with up-regulated PCBP2 and miR-195 potentially targeting LOC105061856 and PCBP2 mRNA were selected as candidate resistance-related genes. Three potential regulatory mechanisms were proposed: (1) suppressed cell dehydration mediated by ACLY downregulation, (2) inhibited aerobic respiration through miR-195-targeted suppression of LOC105061856 and (3) enhanced antioxidative capacity via PCBP2 upregulation despite miR-195's targeting effect. These coordinated adaptations may collectively constitute the molecular basis for camel renal medulla's remarkable water-deprivation tolerance (Zhang *et al,* 2020).

Two copies of CYP2E (CYP2E1 and CYP2E2) , along with CYP2J can help to transform arachidonic acid into19(S)-HETE, whereas CYP4F and CYP4A help to transform it into 20-HETE. Notably, 19(S)-HETE acts as a potent vasodilator in renal preglomerular microvessels and has been shown to promote water reabsorption through tubular mechanisms (Carroll *et al,* 1996; Saadeldin *et al,* 2020).

Dietary salt intake is closely linked to human health, with excessive sodium consumption being associated with increased risks of stroke and cardiovascular diseases. Investigations into the renal medulla of salt-tolerant camels may reveal critical mechanisms underlying high salinity resistance. Through fluorescence in situ hybridisation and dual-luciferase reporter assays, we demonstrated that the long non-coding RNA LNC003834 binds to miRNA-34a, thereby alleviating miRNA-34a-mediated suppression of SLC14A1 mRNA - a transcript encoding a salt absorption inhibitor. These findings suggest that the LNC003834 - miRNA - 34a - SLC14A1 axis functions as a competing endogenous RNA (ceRNA) network (SLC14A1 mRNA, LNC003834 and miRNA-34a) and antioxidant genes (SLC6A1, PCBP2 and PEX5L) (Zhang *et al,* 2020).

Metabolic Adaptation

Metabolic adaptation is mediated through ncRNAs that orchestrate lipid and carbohydrate metabolic reprogramming, thereby optimising energy efficiency under nutrient deprivation. These regulatory molecules can simultaneously inhibit glycolytic pathways while promoting β-oxidation, enabling organisms to maintain energy homeostasis while conserving water reserves. Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors of the nuclear receptor super family and regulate the expression of specific target genes such as those involved in energy and lipid metabolism (Makishima, 2005). Specifically, PPARα is highly expressed in the liver, brown adipose tissue (BAT), heart, skeletal muscle and kidney, which are the tissues that have high capacity for fatty acid oxidation (Takada and Makishima, 2020). lncRNAs and miRNAs activates PPARα/γ to drive fatty acid oxidation in the hump, producing metabolic water during drought while supplying energy for ion-pumping during salt stress. may regulate genes like PPARγ to enhance fat storage in the hump. This fat, when metabolized, produces metabolic water, crucial during droughts.

miR-33, an important regulator of lipid metabolism, target genes involved in metabolism and resulted in improved mitochondrial function and reduced oxidative stress. The reduction in lipid accumulation and liver injury resulted in decreased YAP/TAZ pathway activation, which may be involved in the reduced hepatocellular carcinoma (HCC) progression in livers (Fernández-Tussy *et al,* 2024). It Inhibits SREBP1 (sterol regulatory element binding protein 1) and its downstream lipogenic enzymes in HCC cells via c-Myc. Moreover, SREBP1 is crucial for ACSL4-mediated regulation of lipogenesis as well as HCC cell proliferation and metastasis, This metabolic reprogramming appears to redirect cellular energy resources toward maintaining osmotic equilibrium (Chen *et al,* 2021).

lncRNA UT-AS1 stabilises UT-A1/2 transcripts in renal tissue, enabling urea recycling to concentrate urine (water conservation) and maintain nitrogen balance under high salt intake. the activity of genes in cytochrome P450 (CYP) family are involved in the metabolism of arachidonic acids (KEGG pathway accession code 00590). CYP2J2 is regulated by high-salt diet and its suppression can lead to high blood pressure. Camels are known to be able to take in a large amount of salt apparently without developing hypertension, perhaps because they have more copies of CYP2J genes (Zhao *et al,* 2003).

Evidence from dN/dS-based tests and gene family evolution revealed complex features of adaptation in both Bactrian (*Camelus bactrianus*) and

Dromedary camels (*Camelus dromedarius*), including strong selection in genes from the insulin-signaling pathway regulation, lipid and water metabolism, stress responses to heat, UV radiation and airborne dust (Rocha *et al,* 2021).

AMPK is a critical cellular energy sensor that mainly functions as a metabolic checkpoint to restore energy balance under various metabolic stress conditions (Hardie *et al,* 2012). AMPK is activated by phosphorylation, which maintains cellular energy balance, redox homeostasis and cell survival by regulating glycolysis, fatty acid metabolism, antioxidant reactions and other processes (Lin and Hardie, 2017; Herzig and Shaw, 2018). Liu *et al* (2016) proposed a feed-forward model of NBR2-AMPK regulation, in which the lncRNA NBR2 was induced by the liver kinase B1 (LKB1)-AMPK pathway under energy stress and in turn NBR2 interacted with AMPK and promoted its phosphorylation.

The physiological experiments demonstrated that the elevated blood glucose in camels may be caused by their strong capacity for insulin resistance (Guo *et al,* 2021). Consistent with this argument, numerous rapidly evolving camel genes are functionally associated with both Type II diabetes mellitus (KEGG:04930) and the insulin signaling pathway (KEGG:04910). Specifically, insulin (INS) binding to its receptors induces tyrosine phosphorylation of insulin receptor substrates (IRSs). This phosphorylation cascade subsequently activates PI3K and AKT kinases, initiating downstream processes that facilitate glucose uptake followed by storage (Muoio and Newgard, 2008; Turewicz *et al,* 2025).

Oxidative Stress Adaptability

Oxidative stress resilience is achieved through ncRNA-mediated regulation of antioxidant defenses. High salt intake triggers oxidative damage by disrupting this balance. miRNAs may upregulate antioxidant enzymes by suppressing inhibitors like KEAP1 (which represses Nrf2). Genes encoding antioxidative transcription factors, including Nrf2 (Wang *et al,* 2016), heat shock factor-1, activator protein-1 complex, p53, nuclear factor-kB and signal transducer and activator of transcription 4 exhibited upregulation in the water-restricted renal medulla. This transcriptional reprogramming was complemented by the induction of 14 heat shock genes (HSGs) (Burg *et al,* 2007). miRNAs may inhibit repressors of Nrf2 by targeting KEAP1, boosting antioxidant enzymes to counter salt-induced ROS. Nrf2 is a transcription factor that activates antioxidant genes, mitigating oxidative damage during dehydration (Wang *et al,* 2016).

Under salt stress conditions, the renal medulla of camels exhibited differential expression of 22 mRNAs, 2 lncRNAs and 31 miRNAs compared to the free salt-intake diet group. The lncRNA *LNC003834 binds to miRNA-34a,* thereby relieving suppression of the salt-absorption-inhibiting *SLC14A1* mRNA from miRNA-34a. This suggests that the lncRNA-miRNA-mRNA act as competing endogenous RNAs (ceRNAs). *SLC6A1, PCBP2* and *PEX5L* were shown to enhance the antioxidant capacity of camel renal medulla cells by reducing reactive oxygen species (ROS) levels. These results indicate that that camels achieve sodium homeostasis through regulating the expression of salt-reabsorption-related genes in the renal medulla, involving ceRNAs (*SLC14A1, LNC003834* and *miRNA-34a*) and antioxidant genes (*SLC6A1, PCBP2* and *PEX5L*) (Zhang *et al,* 2020).

Oxidative stress promotes lipid peroxidation and the formation of pro-inflammatory isolevuglandins (IsoLG). lncRNAs, which play a crucial regulatory role in gene expression, including vascular endothelial cells and immune cells. In hypertension, the decreased transcriptional activity of nuclear factor erythroid 2-related factor 2 (Nrf2 or Nfe2l2) correlates with heightened oxidative stress in antigen-presenting cells (APCs) and impaired control of various antioxidant genes (Khan *et al,* 2024).

Camel-Specific ncRNA Innovations

Camel-specific ncRNAs play integral roles in their legendary resilience by orchestrating gene regulatory networks that manage osmotic stress, conserve water and sustain metabolic function.For example, the camelid-specific miR-2434 exhibits multifunctional regulation: it targets SLC12A3 to suppress renal sodium reabsorption while inhibiting AQP3 expression in kidneys to minimise water loss. miR-2434 is implicated in regulating antioxidant pathways, though its direct link to Nrf2/KEAP1 remains uncharacterised. It may interact with stress-responsive genes in a tissue-specific regulatory effects through interactions with stress-responsive genes (Wang *et al,* 2022).

ncRNAs contribute to camels' drought resilience through multi-level regulatory mechanisms involving metabolic modulation, osmoregulation and stress response pathways. ncRNAs play a pivotal role in the drought adaptation mechanisms of camels through various regulatory processes. These insights

underscore ncRNAs' evolutionary significance in desert adaptation, particularly highlighting, the need for functional characterization of camel-specific ncRNAs and the investigation of their interactive networks with both upstream and downstream proteins.

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