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Review

RNA signaling in cellular plasticity during homeostasis and regeneration

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Cells and tissues constantly read and broadcast information through RNA. This mini-review explores how endogenous and damage-released RNAs act as instructive signals that rewire cell identity during steady-state homeostasis and injury repair. We will cover how repetitive-element-derived RNAs and regulatory long-noncoding RNAs (lncRNAs) tune stem and progenitor plasticity in hematopoietic, pluripotent, and muscle systems by coupling stress sensing to cell-fate decisions. We will also outline extracellular dsRNA/TLR3 signaling and injury-induced lncRNAs in epithelial, neural, cardiac, and vascular regeneration, and show how extracellular RNA shapes inflammatory and stromal responses. Together, these concepts present RNA as an active rheostat of cellular plasticity across development, tissue maintenance, and regeneration.

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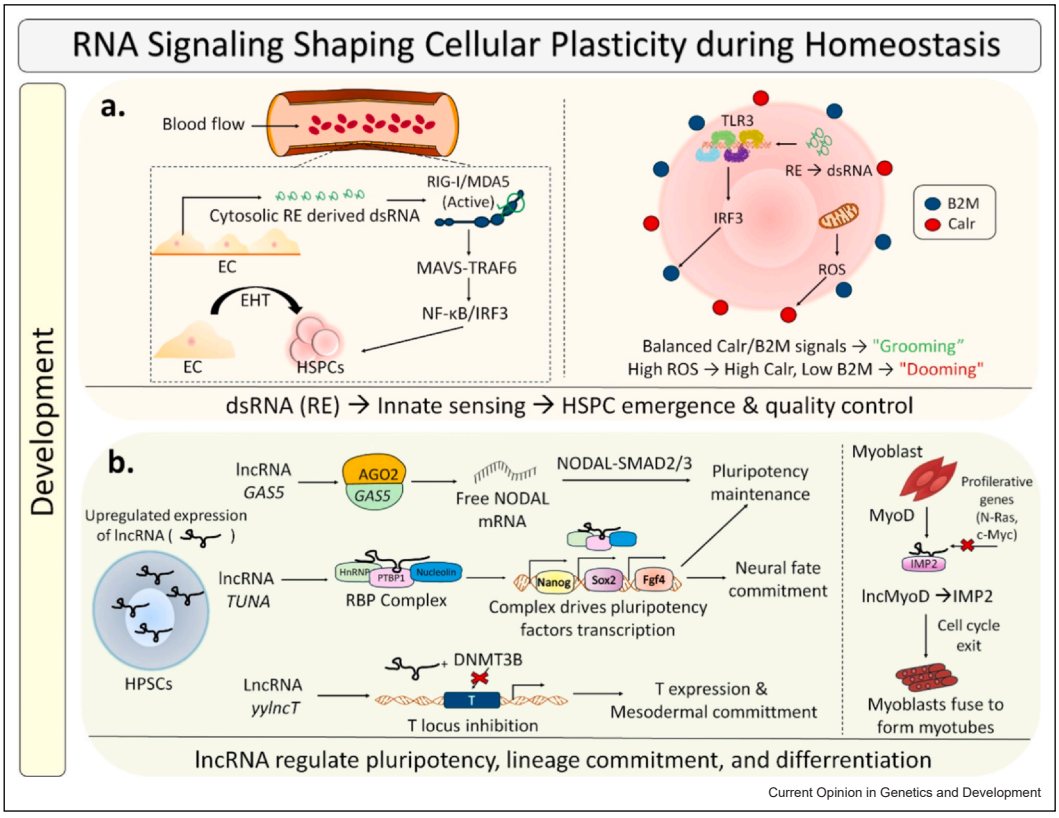
Introduction

Stable RNA species, such as double-stranded RNA (dsRNA), can function as long-lived and long-range signals that influence cellular plasticity during development, disease, and tissue repair [1–3]. These dsRNAs can be produced cell-autonomously through transcription of genomic repetitive elements (RE) or mitochondrial sequences, and their levels are tightly regulated to prevent activation of the integrated stress response via protein kinase or inflammatory pathways mediated by innate RNA sensors, including Toll-like receptor 3 (TLR3), Melanoma differentiation-associated protein 5 (MDA5), and Retinoic acid-Inducible Gene I (RIG-I), as well as the downstream adapter and signaling hub Mitochondrial Antiviral Signaling Protein (MAVS) [4,5]. However, excessive cellular stress can overwhelm these quality-control mechanisms, triggering inflammatory responses. Intriguingly, dsRNAs also belong to the class of Damage-Associated Molecular Patterns (DAMPs), molecular signals of cellular injury that are released upon stress or damage [6]. In response to such conditions, DAMP RNAs may be expelled as naked molecules, RNA–protein complexes, or encapsulated within extracellular vesicles. Through these mechanisms, exported or unmasked RNAs act as remarkably stable paracrine signals, engaging receptors to initiate inflammatory programs or modulate homeostatic cellular functions [3,7,8]. Here, we define RNA signaling broadly: beyond secreted DAMPs that activate innate sensors, it also includes dynamically induced RNAs that couple cell stress cues to transcriptional and epigenetic programs that control cell plasticity.

RNA signaling during homeostasis

Endogenous RNAs can act as cellular signals that regulate plasticity during embryonic development and homeostasis. Metabolic stress and the expression of spurious RNA from genomic RE play a central role in hematopoietic stem cell development and maintenance. During zebrafish embryogenesis, the definitive hematopoietic wave generates hematopoietic stem and progenitor cells (HSPCs) via an endothelial-to-hematopoietic transition (EHT) [9]. Expression of RE-derived RNAs tunes the transition of endothelial cells (EC) into hematopoietic stem cells through detection by the cytosolic dsRNA sensors RIG-I, MDA5, and

Figure 1



RNA signaling shaping cellular plasticity during homeostasis. **(a)** During endothelial-to-hematopoietic transition in zebrafish, cytosolic dsRNA-derived RE activate RIG/MDA-5 — MAVS/TRAF6 signaling, resulting in HSPCs emergence. In HSPCs, RE dsRNA-TLR induces B2M ('don't eat-me') to balance reactive oxygen species (ROS) induced Calreticulin (Calr) ('eat-me'), directing macrophages to 'groom' (proliferation/maintenance) rather than 'doom' (phagocytosis) HSPCs. **(b)** In hESCs, lncRNA *GAS5* binds to miRNA silencing complex Argonaute (AGO2) and acts as a miRNA sponge to protect *NODAL* mRNA from *NODAL* targeting miRNA, sustaining pluripotency; lncRNA *TUNA* forms ribonucleoprotein complexes (hnRNP-K, PTBP1, nucleolin) at *Nanog*, *Sox2* and *Fgf4* promoters, regulating pluripotency and neural fate; lncRNA *ylncT* binds to DNMT3B to prevent Brachyury T locus methylation, ensuring mesoderm commitment; LncMyoD binds to IMP2 to prevent proliferation genes translation (*Nras, Myc*), promoting myoblast to myotube fusion. These studies were shown using mice/human systems.

Laboratory of Genetics and Physiology 2 (LGP2, encoded by *DHX58*). Loss of RIG-I or MDA5 decreases HSPC numbers, whereas loss of the negative regulator LGP2 increases them. RIG-I/MDA5 activation triggers MAVS and Tumor Necrosis Factor-Associated Factor 6 (TRAF6)-dependent signaling, inducing Nuclear Factor kappa-B (NF-κB) and Interferon-Regulatory Factor 3 (IRF3), which together control EHT transition [9] (Figure 1a). Beyond HSPC emergence, RNA signaling also shapes clonal stem cell diversity and maintenance in zebrafish [10]. Calreticulin acts as a molecular chaperone that senses misfolded proteins and endoplasmic reticulum (ER) stress, and it also functions as an immune recognition cue at the cell surface, serving as a phagocytic 'eat me' clearance signal recognized by macrophages [10]. In contrast, HSPCs express high levels of endogenous retrovirus and long terminal repeat (LTR)-derived RE that form dsRNA species activating TLR3 signaling, IRF3, and expression of the surface 'don't-eat-me' signal Beta-2-Microglobulin (B2M) [10]. The balance of these cues determines whether macrophage–HSPC interactions lead to 'grooming' (promoting HSPC proliferation/differentiation) or 'dooming' (phagocytosis and clonal elimination). Thus, RNA sensing and signaling support expansion, quality control, and maintenance of the hematopoietic stem cell niche [10] (Figure 1a).

Whereas hematopoietic fate depends on stimulus-responsive transcription of REs that engages innate RNA sensors, pluripotent stem cell maintenance relies on induced long-noncoding RNA (lncRNA) expression, activating transcriptional, post-transcriptional, and epigenetic mechanisms intracellularly. In human embryonic stem cells (hESCs), lncRNA *GAS5* is directly regulated by pluripotency factors OCT4 and SOX2. *GAS5* preserves pluripotency and self-renewal by protecting *NODAL* mRNA from miRNA-mediated silencing

Table 1

Representative examples of RNA-mediated control of cellular plasticity.

Context/Tissue	RNA species/Source	Sensor/Effector	Plasticity outcome	References
Epidermal barrier repair after UVB	UVB-damaged snRNAs (e.g. U1)	TLR3–TRIF–NF-κB	Induces cytokines and barrier-repair genes	[16,20]
Hair follicle neogenesis after wounding	dsRNA from wound tissue	TLR3 → IL-6/STAT3	Reprograms keratinocytes; initiates hair follicle formation	[18]
Keratinocyte reparative switch	lncRNA SNHG26	SNHG26–ILF2	Shifts inflammatory to reparative gene expression	[30]
Acute vs chronic wound response	lncRNAs WAKMAR1/2	E2F1 / NF-κB modulation	Enhance migration; restrain chemokine production	[31,32]
Spinal cord regeneration	Injury-released dsRNA	Endocytosis → TLR3 → SFK	Drives precursor neuron migration	[17]
Cardiac regeneration (medaka)	Injury-induced dsRNA / poly(I:C)	TLR3 innate immune activation	Restores macrophage recruitment and heart regeneration	[27]
Peripheral axon regeneration	GI-SINE (repeat RNAs)	Nucleolin–ribosome complex; AP-1 transcriptional control	Somatic translational shift; regenerative axon growth	[33]
Arteriogenesis after occlusion	Shear-stress-induced exRNA	NRP1–VEGFR2	Drives endothelial activation and collateral growth	[29]
HSPC emergence	RE-derived dsRNA	RIG-I/MDA5/LGP2 → MAVS	Controls EHT and HSPC formation	[9]
HSPC clonal diversity control	Re-derived dsRNA (LTRs, ERVs)	TLR3→IRF3→B2M High ROS→Calr	Balance of Calr/B2M directs macrophage to shape HSPC clonality	[10]
Pluripotency maintenance	lncRNA GAS5	Competes with NODAL-targeting miRNAs	Maintains NODAL–SMAD2/3 and pluripotency	[11]
Mesodermal commitment	lncRNA yylncT	DNMT3B inhibition at T locus	Maintains T expression; drives mesoderm fate	[13]
Myogenesis	lncRNA LncMyoD	LncMyoD–IMP2	Enables myoblast differentiation	[14]
Pluripotency and Neural lineage commitment	lncRNA TUNA	TUNA–RBP complex	Maintains pluripotency and promotes neural fate	[12]

Key examples illustrating how distinct RNA species engage specific sensing pathways to regulate cellular plasticity across tissues, development, and regeneration.

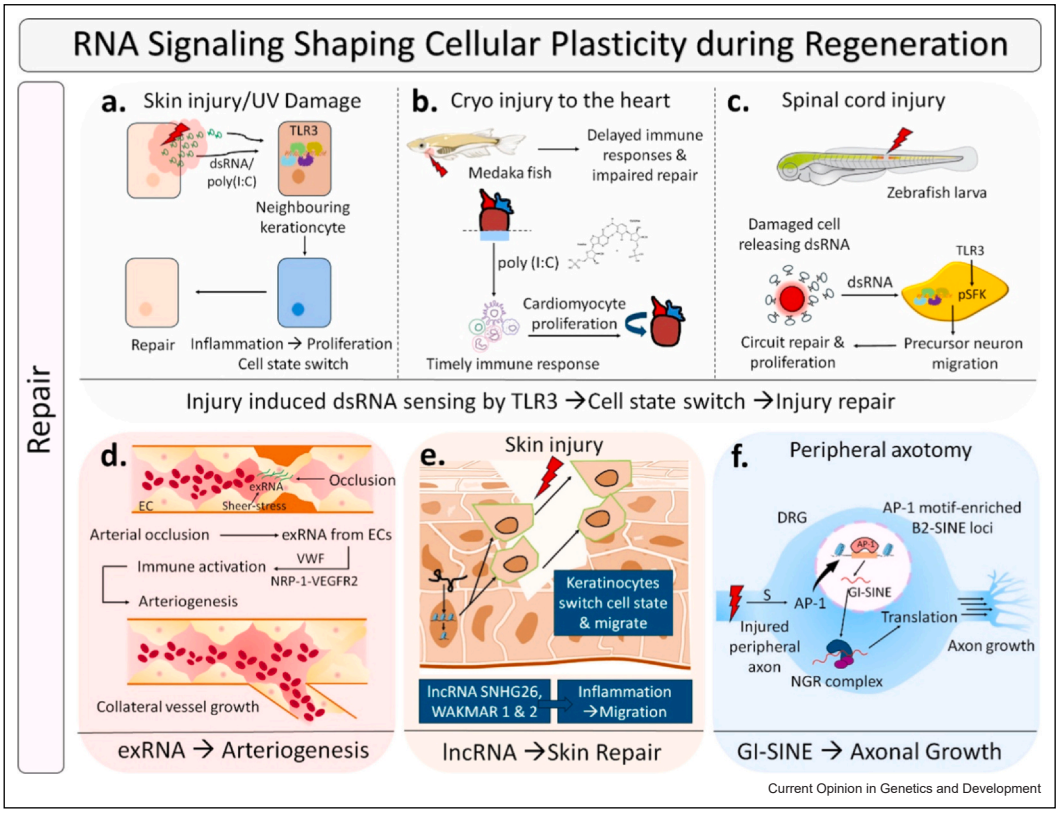
via Argonaute 2 [11]. During differentiation, *GAS5* is downregulated, allowing *NODAL*-targeting miRNAs to accumulate, inhibiting NODAL signaling, and downregulation of core pluripotency factors (OCT4, NANOG) [11] (Figure 1b). Similarly, lncRNA *TUNA* is a context-dependent RNA that regulates both pluripotency maintenance and neural lineage commitment in ESCs [12]. *TUNA* recruits an RNA-binding protein complex (PTBP1, hnRNP-K, and nucleolin) and occupies promoters of pluripotency regulators (*NANOG*, *SOX2*, and *FGF4*), thereby maintaining active histone marks (H3K4me3) and sustaining transcription [12] (Figure 1b). During mesodermal commitment of human pluripotent stem cells, lncRNA *yylncT*, divergently transcribed from the mesoderm regulator Brachyury (*TBXT*) locus, promotes activation of its protein-coding partner by locally inhibiting DNA methylation, preserving accessibility of the *TBXT* locus, and driving the hESC-to-mesoderm transition [13] (Figure 1b). This mechanism seems highly conserved as *yylncT* transcripts are syntenically positioned in both the mouse and human *TBXT* locus.

Muscle formation involves myogenesis, in which muscle stem cells activate and proliferate into myoblasts that then fuse into functional myotubes. During muscle homeostasis and regeneration, lncRNA *LncMyoD* facilitates myoblast differentiation by limiting proliferation and promoting fusion. *LncMyoD* is directly activated by the master transcription factor MyoD, supporting the myoblast-to-myotube transition. In myoblasts, the RNA-binding protein IMP2 (IGF2BP2) binds to its own mRNA and other mRNAs encoding proteins promoting proliferation (e.g. *Nras*, *c-Myc*, *Igf1r*, *Igf2*, *Ccng1*, and *Rhla*) to sustain high IMP2 levels and maintain proliferation. *LncMyoD* competes with these proliferation-promoting transcripts for IMP2 binding, reducing their translation, enabling cell-cycle exit, and permitting fusion into myotubes (Figure 1b). *LncMyoD* knockdown blocks terminal differentiation, while re-expression of mouse *LncMyoD* or the conserved human hLncMYOD rescues differentiation [14] (Table 1).

RNA as a damage and repair signal

Effective tissue repair and regeneration depend on distinct forms of cellular plasticity. In highly regenerative tissues or animal models, repair can be described as comprising 'make do' and 'make new' phases. In the rapid 'make do' phase, diverse resident cells respond to injury signals, gain plasticity, migrate, and remodel the local environment to stabilize the lesion and prepare the tissue for repair. This is typically followed by a 'make new' phase, in which cells with stem and progenitor potential expand, differentiate, and replace the lost tissue.

Figure 2



RNA signaling shaping cellular plasticity during injury. **(a)** dsRNA released from injured mouse skin keratinocytes or dsRNA mimic, poly(I:C), activates TLR3, driving inflammation to proliferation cell state switches that enable epidermal repair and wound-induced hair neogenesis. **(b)** Mechanical injury to zebrafish larval spinal cord releases dsRNA from necrotic cells, activating TLR3 and Src signaling to recruit dormant precursor neurons to the lesion site, restoring neural circuit and later also controlling neural stem cell-driven neurogenesis. (**c**) Exogenous administration of poly(I:C) accelerates immune responses in the normally non- regenerative medaka heart, reducing scarring and enhancing cardiomyocyte proliferation. **(d)** Retrograde injury signals (S) from peripheral axons activate AP-1 transcription factors (including ATF3) in the dorsal root ganglion (DRG) soma (mice), opening chromatin at AP-1 motif-enriched intergenic B2-SINE loci, leading to transcription of GI-SINE. GI-SINE binds to nucleolin (at the glycine-arginine-rich domain) and ribosomal subunits, in the soma, that shifts translation of cargo mRNAs (Importin-β1, mTOR) from distal axonal tips to soma, promoting regenerative axon growth. **(e)** Following skin injury in humans/mice, lncRNA SNHG26 in keratinocytes interacts with ILF2 to redirect inflammatory to migratory gene loci, enabling migration of keratinocytes; *WAKMAR 1/2* drives migration of keratinocytes through epigenetic and anti-inflammatory mechanisms, respectively, and together these lncRNAs enable re-epithelialization. **(f)** Arterial occlusion triggers exRNA release from vascular EC, interacting with VEGFA coreceptor, NRP1, to enhance VEGFR2 signaling to recruit macrophages, thus arteriogenesis restoring perfusion (mice).

Early after injury, endogenous RNAs secreted or released from damaged or necrotic cells act as DAMPs that locally rapidly initiate inflammatory signaling pathways that regulate cell plasticity and tissue remodeling required for repair [8]. In particular, extracellular dsRNA and its interaction with the cognate receptor TLR3 function as a sensor of tissue damage and a potent modulator of repair responses [15–17]. For example, dsRNA release is pivotal in skin, spinal cord, and heart repair, and removal of extracellular dsRNA using RNases after injury markedly attenuates or abolishes repair responses [17–19]. Conversely, repair programs that activate cellular plasticity can be stimulated by the synthetic dsRNA analog Poly(I:C) [17,18].

Ultraviolet-B (UVB) exposure from sunlight or artificial sources induces keratinocyte damage and extracellular release of structurally altered small nuclear RNAs (snRNAs), primarily U1 snRNA, along with other snRNAs and scaRNAs in mice. These RNAs form double-stranded stem-loop structures and are taken up by neighboring undamaged keratinocytes via scavenger receptor-mediated endocytosis [16,20]. Within endosomes, TLR3 recognizes dsRNA and activates the canonical TLR3–TRIF pathway, leading to NF-κB activation and production of inflammatory cytokines such as Tumor Necrosis Factor alpha (TNF-α) and Interleukin-6 (IL-6) [16] (Figure 2a). Beyond inflammation, TLR3-mediated dsRNA sensing orchestrates

functional barrier repair of the skin [14]. UVB-damaged keratinocytes release dsRNA that engages TLR3 and upregulates genes critical for barrier restoration, including lipid metabolism enzymes (*ABCA12*, *GBA*, *SMPD1*), structural proteins (*TGM1*), and junctional components (*CDSN*, *OCLN*, *TJP1*, *CLDN1*). Thus, dsRNA–TLR3 signaling coordinates the transition of keratinocyte function from maintenance to barrier restoration during repair. Consistent with this, administration of the dsRNA agonist Poly(I:C) induces epithelial plasticity by tightening barrier function through reinforcement of tight junctions and by altering functional properties, such as increasing transepithelial electrical resistance and reducing paracellular permeability. *In vivo*, UVB-exposed TLR3-deficient mice exhibit delayed recovery and develop chronic non-healing wounds due to impaired epidermal barrier restoration [20] (Figure 2a). Collectively, these findings demonstrate that dsRNA release and sensing are critical for effective epidermal repair. The TLR3–dsRNA signaling axis functions not only as a barrier repair mechanism after mild damage, such as UVB exposure, but also in severe full-thickness skin wounds that require complete regeneration of epidermal cell types and hair follicles. dsRNA released by injured keratinocytes activates TLR3, inducing IL-6-driven phosphorylation of Signal transducer and activator of transcription 3 (STAT3), which is essential for initiating gene programs that control keratinocyte reprogramming and hair follicle neogenesis during regeneration in mice [18] (Figure 2a). TLR3 activation fundamentally reprograms keratinocytes from their normal differentiation trajectory into a progenitor-like state capable of hair follicle formation. Notably, TLR3 is dispensable for embryonic hair follicle development and growth. However, activation of the TLR3–IL-6/STAT3 pathway by the synthetic dsRNA analog Poly(I:C) suppresses keratinocyte differentiation markers (*Krt1*, *Flg)* and promotes expression of hair progenitor-associated markers (*Lgr5*, *Lgr6*, *Krt15*, *Cd200*). This reprogramming is accompanied by a striking morphological shift toward a migratory, wound-responsive phenotype. Upregulation of hair progenitor markers further activates developmental signaling pathways, including WNT, SHH, and EDAR, which drive embryonic hair follicle morphogenesis. Thus, TLR3 signaling actively reprograms keratinocytes to change cell fate, recapitulating developmental programs during embryogenesis [18]. Importantly, these findings indicate that while TLR3 activation is necessary for hair regeneration, it's not sufficient on its own, and the wound microenvironment provides essential additional cues.

While zebrafish can regenerate its central nervous system (CNS), heart, and retina [21–24], a commonly used strain of medaka, another teleost fish similar to zebrafish, lacks the ability to regenerate these tissues [25,26]. Comparative transcriptomic analyses of cardiac cryoinjury in zebrafish and medaka showed dysregulated Toll-receptor signaling, including components of the TLR3 pathway, in the non-regenerative medaka [27]. Further investigation showed that acute immune responses in medaka were delayed and attenuated, characterized by reduced macrophage recruitment, impaired cardiomyocyte proliferation, and incomplete scar resolution. Remarkably, administration of Poly(I:C) after cardiac injury in medaka enhanced immune activation, promoted macrophage recruitment, and restored cardiomyocyte proliferation and scar resolution, ultimately enabling regeneration of cardiac tissue [27] (Figure 2b). Timely macrophage recruitment appears critical for coordinating regeneration, as macrophage depletion in zebrafish results in scarring and impaired heart regeneration, phenocopying the non-regenerative response observed in medaka [27].

Injury-induced extracellular RNA (exRNA) serves as a pivotal local damage signal that initiates repair after spinal cord injury in zebrafish. Following injury, dsRNA released from damaged or necrotic cells promotes tissue remodeling and recruits immature precursor neurons to the lesion site [17] (Figure 2c). At later stages, dsRNA also activates quiescent neural stem and progenitor cells. The migrating immature precursor neurons pioneer the initial functional circuit regeneration, restoring neural activity and motor function. Removal of dsRNA using RNase H blocks circuit restoration, whereas stimulating the response with Poly I:C enhances it. Extracellular dsRNA, either naked or encapsulate is thought to enter cells via Scavenger A receptors and activate cytosolic sensors such as MDA5 or RIG-I as well as downstream targets including TANK-binding kinase 1 (TBK1), which triggers a type I interferon response [28]. Interestingly, blockade of scavenger receptors or TBK1 does not impair repair, whereas inhibition of endocytosis or TLR3 function disrupts spinal cord regeneration, suggesting that dsRNA uptake via endocytosis is critical. The binding of dsRNA to TLR3 is highly dependent on an acidic environment, and the low extracellular pH detected after spinal cord injury facilitates dsRNA-TLR3-mediated repair. Quantification of the pH gradient and dsRNA/TLR3 signaling range indicates that dsRNA acts as an early key damage signal and a spatiotemporal mediator of spinal cord repair. Intriguingly, the early phase of tissue remodeling does not rely on canonical TLR3 signaling, which typically activates the type I interferon and NF-κB pathways. Instead, dsRNA–TLR3 interaction directly phosphorylates Src-family kinases expressed by immature precursor neurons and is required for their migration [11]. Endogenous exRNA also coordinates vascular repair following arterial occlusion, where rapid restoration of blood flow is critical (Figure 2d). After blockage, increased shear stress triggers endothelial cell release of exRNA, which interacts with the VEGFA co-receptor NRP1 and, in turn,

enhances VEGFR2 signaling. Enhancing VEGFR2 signaling stimulates local release of von Willebrand factor and initiates arteriogenesis that bypasses the occlusion [29]. Collectively, these findings demonstrate that dsRNA and TLR3 signaling play essential roles in tissue repair.

Injury can also induce expression of lncRNAs and cell-autonomous changes in plasticity without secretion or release by integrating stress response to gene regulation. For example, injury-induced expression of the lncRNA *SNHG26* in keratinocytes at the wound edge plays a pivotal role in tissue remodeling, wound closure, and re-epithelialization. *SNHG26* interacts with the RNA-binding transcription factor ILF2, switching gene expression from inflammatory mediators (*JUN*, *IL6*, *IL8*, *CCL20*) to genes regulating cell adhesion, migration, and proliferation, such as *LAMB3* [30] (Figure 2e). Additionally, injury-induced TGF-β signaling regulates the expression of lncRNAs *WAKMAR1* and *WAKMAR2*, which are required for re-epithelialization during skin repair [31,32]. *WAKMAR1* inhibits DNA Methyltransferase (DNMT)-mediated methylation of the *E2F1* promoter, activating genes involved in cell migration and thereby promoting keratinocyte migration and wound closure [31]. Furthermore, *WAKMAR1* negatively regulates inflammatory chemokine production via the NF-κB signaling pathway [32] (Figure 2e).

Peripheral axons can regenerate after axotomy, whereas CNS axons cannot. Following sciatic nerve injury in mice, retrograde signals from the damaged axon activate the AP-1 transcription factor complex in the neuronal soma. The AP-1 transcription factors translocate to the nucleus and remodel chromatin, enabling injury-induced transcription of intergenic B2-short interspersed nuclear elements (B2-SINEs) via AP-1 motif-rich enhancers [33]. The resulting growth-inducing B2-SINE (termed GI-SINEs) RNAs interact with the RNA-binding protein Nucleolin, sequestering the Nucleolin–ribosome complex in the soma. This redistribution shifts translation of growth-promoting signals, such as mTOR, from the distal axon to the cell body, thereby driving axon outgrowth (Figure 2f). Strikingly, exogenous expression of B2-SINEs in regeneration-incompetent CNS neurons, such as retinal ganglion cells and corticospinal tract neurons, is sufficient to promote axon regeneration, demonstrating that RE-derived RNAs function as injury-responsive regenerative signals [33] (Figure 2f; Table 1).

Conclusion

RNA is not just a readout of cell state — it is also a signal that shapes it. Across injury and homeostasis, exported or unmasked RNAs (especially dsRNA and lncRNAs) act as durable, paracrine cues that couple stress sensing to fate decisions. In the steady state, RE RNAs and regulatory lncRNAs tune stem and progenitor plasticity. On the other hand, damage-released dsRNA can engage TLR3 to coordinate inflammation with repair programs, while injury-induced lncRNAs rewire gene expression to enable migration, re-epithelialisation, and regeneration. Together, RNA functions as an active rheostat linking damage, immunity, and identity.

Looking ahead, key open questions in this field include how cells can distinguish endogenous from foreign or mis-localized RNA, how non-regenerative tissues or species fail to decode similar RNA signals into pro-regenerative programs, and whether tuning specific RNA sensors or pathways can enhance repair in non-regenerative conditions. Addressing these questions will require technologies that can track and define RNA species with spatiotemporal precision *in vivo*, improvements in methods for capturing exRNA and RE RNAs and how they interact with RNA sensors, and understanding the outcomes of the signaling is essential. These approaches should clarify how RNA-sensing circuits are built in different tissues and organisms and how they can be rewired to promote regeneration without activating maladaptive inflammation.

CRediT authorship contribution statement

Ajai Chinnaiah Nagaraj: Conceptualization, Writing – original draft, Writing – review and editing, Visualization, Validation. **Ehsan Pahsay Ahi:** Writing – review and editing, Validation. **Minna-Liisa Änkö:** Writing – review and editing, Validation, Resources, Funding acquisition. **Jan Kaslin:** Conceptualization, Writing – original draft, Writing – review and editing, Validation, Resources, Funding acquisition.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

None.

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