Non-coding RNA Research 3 (2018) 39–41

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: http://www.keaipublishing.com/NCRNA

Non-coding RNA function in stem cells and Regenerative Medicine

Regenerative Medicine, the concept of repairing human organs to restore their normal function, has captivated humanity since ancient times. In Greek mythology, the titan Prometheus helped mankind with fire stolen from Mount Olympus, home of the Gods. As punishment, Prometheus was shackled to Mount Caucasus where each day Zeus would send his eagle down to devour his liver. Part of the macabre torture entailed that Prometheus' liver grew back each night to ensure he underwent the same ordeal the following day. Whether the ancient Greek understood that certain organs possess endogenous capacity for self-repair or the legend merely serves as an allegory to an individual's suffering and rebellion against a government or an accepted practice, likely remains nurture for literature debate, but the imagery of a suffering hero with a regenerating organ appeals to a scientist's imagination.

Earthworms, starfish, lobsters, snails, salamanders and zebrafish can replace complete organs or limbs after amputation [1]. Mammalian species possess a far more modest ability to regenerate tissues, but still rebuild themselves at the cellular level, fix damage and heal wounds of organs that contain pools of stem cells. The possibility to generate suitable cell types for therapeutic use has been facilitated by the revolutionary idea to use stem cells as regenerative starting point. Even in organs virtually devoid of meaningful numbers of stem cells or progenitors, e.g. the adult heart, brain or retina, the same concepts in stem cell biology of pluripotency, cellular reprogramming, and lineage-specific differentiation seem applicable to stimulate somatic cell types to evoke repair of stem cell-devoid organs [2]. A better understanding of the biological principles that are fundamental to physiology and stem cell biology may aid to generate breakthroughs in our regenerative toolbox. In that context, new concepts are likely to derive from a better understanding of our genome. The results of the Encyclopedia of DNA Elements (ENCODE) project show that about 80% of our genome is functional, has a regulatory role, and is transcribed into various classes of non-coding, regulatory RNAs (https://www.encodeproject.org). Thus, the next frontier in Regenerative Medicine is this vast territory of the genome that does not directly encode proteins but instead has regulatory functions. A deeper understanding of the regulatory functions of the non-coding part of our genome may shed light on the mechanisms that define cellular plasticity, pluripotency and differentiation and will eventually transform current medicine towards more personalized disease diagnostics and therapies.

In this special issue of Non-Coding RNA Research, many pioneering scientists have contributed their insights in the current state-of-the-art of non-coding RNAs and where therapeutic opportunities could be found that are relevant to regenerative approaches. For example, Wang and colleagues [3] remind us that long non-coding RNAs (lncRNAs) are essential for the life cycle of the simplest of organisms such as viruses, indicating their ancient evolutionary heritage. Indeed, lncRNAs are functionally involved in virtually every step of viral gene expression, replication, genome packaging, virion release, viral latency and viral transformation [4]. On top of that, it now has become clear that lncRNAs suppress the host antiviral innate immune response [5]. In contrast to proteins that function in viral infection, lncRNAs are expected to be novel targets for the modulation of all types of biochemical processes due to their broad function and intimate relationship with the very survival of viruses. Since the viral life cycle and the mechanism of the host antiviral response are sensitive to CRISPR/Cas9 genome editing of viral genomes [6], targeting lncRNAs by genome editing could yield unexpected yet attractive prophylactic or therapeutic spinoffs in the treatment of viral diseases.

Luginbühl and colleagues [7] give an overview of our state of knowledge how microRNAs and lncRNAs - either in combination with specific sets of transcription factors or completely on their own – can reprogram fully differentiated mature cells into induced pluripotent stem cells (iPSCs) or can evoke transdifferentiation into cells into a different lineage. As more mechanisms of non-coding RNAs are revealed, additional opportunities to devise techniques to generate high quality iPSCs and directly converted cell types will become prevalent, eventually accelerating the application of reprogrammed cells in the clinics.

An unexpected venue where non-coding RNAs and stem cells meet, relate to the concept that non-coding RNAs may provide attractive targets for stem cell-based cancer therapies. In the last decade, the term “cancer stem cell” was defined as a cell within a tumor that possesses the capacity to self-renew and to form heterogeneous lineages of cancer cells that consist of the tumor [8]. Sakamoto and colleagues [9] demonstrate that accumulating evidence has provided insights into the importance of microRNAs such as miR-200 cluster members as regulators of carcinogenesis, cancer invasion, and metastasis [10]. Likewise, the involvement of disease- and kidney-specific TGF-β1- dependent lncRNAs has been recognized in renal cell carcinoma, renal inflammation, renal injury and fibrosis [11]. For example, lncRNA MEG3 is reduced in biopsies of patients with renal cell carcinoma and overexpression of lncRNA MEG3 confers resistance to mitochondrial-dependent apoptosis [12]. Conversely, lncRNA RCCRT1 is found overexpressed in human renal cell carcinomas and is associated with lower survival after surgery, while RCCRT1 silencing in renal cell carcinoma cells revealed its involvement in the proliferation, migration, and invasion of the cancer cells [13].

Skeletal muscles have an impressive capacity to regenerate due to a specialized reservoir of muscle specific stem cells, also known as satellite cells. Quiescent in uninjured muscles, satellite cells become quickly activated, proliferate and differentiate into

https://doi.org/10.1016/j.ncrna.2018.04.004

myotubes following skeletal muscle injury using well-established transcriptional mechanisms involving the myogenic regulatory factors of the MyoD family [14]. Gonçalves and Armand [15] provide an excellent description how our understanding of each step of muscle regeneration - inflammation, regeneration and maturation - is expanded by an interconnectivity between classical myogenic transcriptional regulators and an expanding range of non-coding RNAs. The essential function of non-coding RNAs in muscle regeneration is demonstrated by the function of the imprinted gene encoding the H19 lncRNA, which is highly expressed in satellite cells [16]. Mice carrying a targeted deletion of the H19 gene present a 50% loss of satellite cells in adult muscles, suggesting that H19 is required for the quiescent state of satellite cells. Two myogenic microRNAs, miR-208b and miR-499, reinforce slow-muscle gene expression by directly repressing translation of the transcriptional repressors Sox6, Purb, Sp3 and HP-1b during maturation of regenerating myofibers [17]. And finally, slow genes are silenced in fast myofibers by Linc-MYH, a lncRNA embedded within the cluster of fast MYH genes and required for full expression of fast genes [18].

An organ with notoriously low regenerative potential is the heart. Already a few hours after a heart attack, a loss of 25% of the total amount of heart muscle cells present in the left ventricle can be observed and are eventually replaced by a non-contracting scar. Hence, to solve this large biomedical driver of cardiovascular disease, researchers are testing an array of solutions, ranging from *ex vivo* cell therapy strategies based on the direct delivery of regenerative cells isolated from different sources (e.g. induced pluripotent stem cells, embryonic stem cells, bone marrow, liposuction or heart biopsies) [19], to tissue engineered implantations of functional patches [20], to the *in vivo* stimulation of resident cell sources by delivery of reprogramming factors [21] or inducers of cardiomyocyte cell-cycle re-entry [2]. Choong and colleagues [22], Garreta and colleagues [23] and Raso and Dirkx [24] discuss in this Special Issue the progress made in these various therapeutic approaches to accomplish cardiac regeneration, each review focusing on the peculiars for slightly different approaches.

Apart from providing state-of-the-art review articles by carefully selected international experts, we are very pleased to enlist original, experimental work in this Special Issue, exemplifying the high pace at which new breakthroughs in this field are realized. Duygu and colleagues [25] focus on adverse cardiac remodeling that occurs after myocardial infarction and the molecular actors that play a role in this process. The authors focus on a previously discovered stress-dependent microRNA, miR-199b-5p, which is sufficient to activate calcineurin/NFAT signaling, leading to exaggerated cardiac pathological remodeling and dysfunction [26]. The expression of miR-199b is elevated in the post-infarcted heart. Transgenic mice with cardiomyocyte-restricted overexpression of miR-199b-5p displayed exaggerated pathological remodeling after myocardial infarction, reflected by severe systolic and diastolic dysfunction and fibrosis deposition. Conversely, therapeutic silencing of miR-199b-5p in post-infarcted hearts with an antagomir to specifically inhibit endogenous miR-199b-5p *in vivo*, resulted in efficient suppression of cardiac miR-199b-5p expression and attenuated cardiac dysfunction and dilation following MI. Editing this Special Issue was very rewarding. We hope that reading the papers will be even more stimulating, and will help to fuel even more attention to the interplay between discoveries in the non-coding genome as a fascinating facet of Regenerative Medicine.

Acknowledgements

L.D.W. acknowledges support from the Netherlands CardioVascular Research Initiative: the Dutch Heart Foundation, Dutch Federation of University Medical Centers, ZonMW and the Royal Netherlands Academy of Sciences. L.D.W. was further supported by grant 311549 from the European Research Council (ERC) and a VICI award 918-156-47 from NWO.

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Available online 20 April 2018