Editorial

MicroRNAs—getting the hang of it

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Following their discovery in *C. elegans* in 1993¹ and subsequent ‘rediscovery’ in 2001, microRNAs (miRNAs) have been intensively studied and currently more than 31 000 scientific papers have been published on the subject. So, a massive amount of information has been gathered on the expression and biological impact of miRNAs in normal physiological processes and in pathologies and we understand much more about the mechanisms underlying miRNA-mediated gene regulation. In addition, strategies for exploiting miRNAs as biomarkers and therapeutic targets are beginning to mature.

This issue of *Cell Death and Differentiation* features a series of interesting reviews on miRNAs focusing on the mode of action, their involvement in stemness, and their usefulness as markers and in novel therapies (Figure 1). Also in this issue, in their News and Commentary, Amelio and Melino² briefly summarize the recent advances on the CRISPR technology, which promises to be a uniquely useful tool in both basic and applied research. Aside from the potential impact, this technology may get on genetic modification of foodstuffs and in treating human genetic diseases, the CRISPR system has already proven itself a very versatile tool that aside from gene modification may be adopted to increase or diminish gene expression, to purify specific chromatin domains or to fluorescently label single genomic loci. I imagine that the Nobel committee will be following this development closely.

Wilczynka and Bushell³ review our current knowledge on how miRNAs mediate target repression. In recent years, much effort has been put into establishing a unified model for miRNA-mediated repression and the current evidence suggest a two-step model in which initial translational repression^{4,5} is followed by transcript deadenylation and destabilization.^{6,7} As pointed out by Wilczynka and Bushell, several questions remain to be answered: are all miRNA targets bound by the same protein complex or do RISC complexes come in different flavors with different functionalities? To what extent is miRNA-mediated repression reversible and how is this regulated in the cell? How does miRNA-mediated repression interplay with other regulatory mechanisms such as various RNA modifications? Clearly, there is still a lot to learn.

The skin is the body’s first barrier to the outside world and has proven a valuable model system for understanding stemness and differentiation processes. p63, a member of the p53 family of transcription factors, is a master regulator of

epidermal homeostasis and is integrated in an intricate network with several miRNAs and miRNA-processing factors to regulate epithelial stemness and cell-fate decisions. The existence of several p63 isoforms further complicates the network, and Melino and coworkers⁸ review this network and the links to epidermal senescence and cancer. Interestingly, p63 also interplay with the better-characterized p53 tumor suppressor, and mutant p53 has also been linked to stemness.⁹ Importantly, the authors point out a number of open questions, such as how the different p63 isoforms contribute to epidermal homeostasis? In extension, can the network miRNAs constitute new biomarkers or even therapeutic targets in epithelial cancers?

Liver cancer is among the most common neoplasias worldwide and the therapeutic options are currently limited. Negrini and coworkers¹⁰ outline the presently known involvement of miRNAs in proliferation and metastasis processes related to liver cancer and discuss the currently available animal models and their usefulness for testing miRNA-based therapeutic strategies. The authors point to the fact that most genetic mouse models develop liver cancer without passing through liver cirrhosis, which is fundamentally different from the situation in humans, where cirrhosis is present in >80% of patients with hepatocellular carcinoma. Fortunately, the liver can easily be targeted via systemic oligonucleotide-based therapeutic approaches; in fact, avoiding accumulation of anti-miRNAs or miRNA mimics in the liver is a major issue when trying to target pathologies in other organs.¹¹

One of the most clinically promising exploitations of miRNAs is that using extracellular miRNAs, carried in exosomes, as biomarkers for pathologies. Exosomes are extracellular vesicles thought to take part in cell-to-cell communication via delivering a range of molecules including miRNA, although exosome formation may also represent a means for cells to get rid of unwanted molecules. Exosomes are found in various bodily fluids but especially circulating exosomes found in plasma or serum has attracted attention due to the ease by which these can be sampled. Importantly, exosome-derived miRNAs reflect their tissue of origin and tumor-derived exosomes potentially represent a unique source of biomarkers, which in time could revolutionize current diagnostics. Calin and coworkers¹² summarize exosome biogenesis and function and review the current knowledge on exosome miRNAs and how these can be exploited as

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The demonstration that the miR-15/16 cluster is lost in chronic lymphocytic leukemia (CLL) was the first genetic evidence that miRNAs are involved in cancers.¹³ In this issue, Perkarsky and Croce¹⁴ take us through the discovery of the miR-15/16 locus and the role of these miRNAs in CLLs, including the identification of key downstream targets, such as *BCL2* and *WT1*. They further describe the involvement of

All in all, the miRNA field has come a long way but we clearly still have a lot to learn about these fascinating molecules and how they may be exploited.

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