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Short Communication

MiR-302: The Multifunctional MicroRNA

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MicroRNAs (miRNAs) are short single-stranded noncoding RNAs (20- to 25-nucleotide (nt) long) representing a class of small regulatory RNAs. By inhibiting the translation of target mRNAs, miRNAs regulate gene expression posttranscriptionally and thus play an important role in a wide range of cellular processes (1). Currently, there are two known types of miRNAs: intergenic and intronic miRNAs. Biogenesis of an intergenic miRNA starts with the synthesis of a primary miRNA transcript (pri-miRNA) catalyzed by types-II or -III RNA polymerase (Pol-II/III). Pri-miRNAs are processed in the nucleus by the ribonuclease Drosha into a miRNA precursor (pre-miRNA) approximately 60-nt in length. After being transported into the cytoplasm, these pre-miRNAs are further processed into mature and functional miRNAs by the cytoplasmic ribonuclease Dicer (2). Mature miRNAs then associate with a number of proteins to form the RNA-induced silencing complex (RISC) that bind with target mRNAs having total or partial complementary sequences to the miRNAs and initiate the inhibition of subsequent protein translation via RNA interference (RNAi) (3).

Following DNA transcription, a premature messenger RNA (pre-mRNA) strand consisting of introns and exons is synthesized. The introns are removed from the pre-mRNA molecule via RNA splicing and the exons are ligated together to form the mature mRNA for subsequent protein translation. Introns, once thought to be non-essential elements meant to be removed from pre-mRNAs for exons to form mature mRNAs, have now been identified to function as pri-miRNAs that are converted into pre-miRNAs in the cell nucleus by Drosha (4). As in the case with intergenic miRNAs, these intronic pre-miRNAs are then exported to the cytoplasm and processed into mature and functional intronic miRNAs that incorporate into RISC and mediate gene silencing effects via RNAi. MicroRNAs have been shown to play an instrumental role in a wide variety of biological processes including cell cycle regulation, apoptosis, control of metabolic pathways, differentiation and maintenance of pluripotent state (5).

Stem cells have a unique ability to develop into many different cell types in the body and therefore they offer great potentials for cell-based therapy to treat various diseases. Given the ethical and political controversies surrounding research using human embryonic stem cells (hESCs), the involvement of certain miRNAs in pluripotent cell maintenance and renewal sparked a great deal of interest in exploring the plausibility of generating induced pluripotent stem cells (iPSCs) using miRNAs. This is also important since miRNA-induced iPSCs represents an improvement in iPSC generation efficiency over the previously established four-factor-induced iPSCs developed by Yamanaka's group in 2006 (6). The concept of generating iPSC using microRNAs originated from Lin's group in 2008, which presented the first evidence of using an intronic miRNA, miR-302, to reprogram both human normal and skin cancer cells into a hESC-like state (7).

Exclusively and most abundantly expressed in hESCs and iPSCs, the miR-302 familial miRNAs (mir-302s) consists of four sense homologues (miR-302b, c, a and d) and three antisense members (miR-302b*, c* and a*), all of which are concurrently transcribed as a polycistronic RNA cluster along with another miRNA, miR-367 (8). Further studies by Lin and other groups revealed that many of miR-302's targets function as active developmental signals involved in initiation or facilitation of lineage-specific cell differentiation (9). By inhibiting genes essential for embryonic development and cell differentiation, miR-302s reprogram and transform differentiated somatic cells into ES-like pluripotent cells as well as maintaining the long-term pluripotent and renewal properties of these cells (9). Furthermore, Lin's group showed that cells transfected with miR-302 not only express several key ES cells markers such as Oct3/4 and Sox2, but also exhibit a highly demethylated genome similar to a reprogrammed zygotic genome (9). Taken together, the ability of miR-302 to reprogram somatic cells into ES-like pluripotent cells makes this microRNA an attractive tool for early developmental studies as well as a resource for potential applications in cancer therapy and regenerative medicine.

Besides fostering stem cell research, increasing evidence has also shown miR-302 to offer potentials in other applications as well – such as anticancer therapy and wound management care. Cancer is the second leading cause of death in the U.S. In addition to radiation therapy and surgery, treatment with chemotherapeutic drugs such as doxorubicin is the most common and established method for treating patients with advanced cancer. In many cases, however, chemotherapy ultimately fails due to the development of drug resistance and toxicity of the chemotherapeutic drug used in treatment. Along with the finding that cancer therapeutics currently have the lowest clinical trial success rate of all major diseases, identifying new cancer drug candidate(s) that are truly effective and safe is of urgent need. Besides suppressing tumorigenicity through initiating the somatic cell reprogramming process (7) and suppressing the cdk2 and cdk4/6 cell cycle pathways (10), numerous findings have demonstrated miR-302's anti-cancer properties via other mechanisms and therefore making this microRNA an attractive and novel candidate for developing cancer therapy. For example, miR-302b was found to inhibit the growth of human hepatocellular carcinoma both in vitro and in vivo by suppressing the expression of AKT2, a key cell cycle regulator (11) Also, through suppressing proliferation, angiogenesis and invasion, and through reversing the epithelial-to-mesenchymal transition (EMT), miR-302 sensitized melanoma and colorectal cancer cells to hypoxia and also to the selective BRAF inhibitor vemurafenib (12). Data from Jiang's group showed that miR-302 was significantly downregulated in cervical cancer tissues and this is associated with poor prognosis in cervical cancer patients, and restoring miR-302 expression inhibits cell migration and invasion in cervical cancer (13). Furthermore, miR-302 was found to sensitize multidrug resistant breast cancer cells to doxorubicin by suppressing P-glycoprotein through targeting the MAP/ERK kinase kinase 1 (MEKK1)-mediated pathway (14).

Taken together, these findings established miR-302's tumor suppressing properties and strongly suggest that miR-302 may represent an efficient tool for controlling cancer and especially for those with more invasive nature.

Wound healing is the complex biological process by which the skin or other body tissue repairs itself in response to injury or other types of trauma (15). Proper wound care promotes effective wound healing and therefore is an important part of a patient's recovery process. According to reports by Markets and Markets, the global wound care market is currently USD 17.0 billion and expect to rise to USD 20.4 billion by 2021. To address the efficacy of miR-302 in accelerating wound healing, Author has participated in development of a proprietary technology/methodology to grow proprietary Dicer-negative cells expressing miR-302 precursors (P-miR-302) and cost-effectively extract and purify P-miR-302 molecules from these cells. P-miR-302s are hairpin RNA molecules that can be directly processed into mature and functional miR-302s following delivery into the cytoplasm of target cells. For delivery, author has also participated in the development of a proprietary sugar-based solvent, F5, for formulating P-miR-302s, based on glycylglycerins that interact and protect ESC-specific miRNAs, including miR-302, that were identified by Lin et al (16).

Results from a couple of studies, results of which are unpublished, that the author has participated in have established miR-302's efficacy in promoting scar free wound healing. In the first study, open skin wounds were generated by scalpel in the hind legs of albino house mice and treated with F5-formulated P-miR-302s (F6) via topical application. Our results revealed that treatment with F6 reduced the wound size by more than 50% and 80% by days 8 and 11, respectively, as compared to the wounds treated with blank control. In the second study, the objective of which was to assess the efficacy of miR-302 on healing of full-thickness wounds in pigs, open wounds were created on both right and left sides of a group of 2 to 3-month old Landrace pigs and treated once again with F6. Results from this study showed that wounds treated with F6 healed at over twice faster the rate as compared to wounds treated with blank control. In summary, we conclude that miR-302, as a stem cell-specific factor, promotes effective and scar free wound healing and therefore represents a novel repairing and rejuvenation agent in the lucrative wound care industry.

In summary, miR-302 presents a novel and legitimate candidate for nucleic acid-based therapeutics. As some of the currently established findings has shown thus far, it is simply a matter of time before miR-302's vast potentials are realized.

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