



MicroRNAs in the Cholinergic Anti-Inflammatory Pathway: Prospective Therapeutic Targets for Inflammatory Diseases

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Received date: November 21, 2016; Accepted date: November 26, 2016; Published date: December 05, 2016

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Keywords MicroRNA; Cholinergic anti-inflammatory pathway; Inflammatory diseases; miR-124; miR-132.

Running Head: Cholinomirs Potential Therapeutic Targets for Inflammatory Diseases

The host inflammatory response can be self-limited or progress to immunological and inflammatory diseases. It has been well known that humoral anti-inflammatory mechanisms, including IL-10, TGF- β 1, glucocorticoids and other cytokine inhibitors, can protect tissue against cytokine-induced damage in humans. Recent advances have identified a brain to immune system mechanisms, termed cholinergic anti-inflammatory pathway (CAP). Briefly, the vagus nerve senses and conveys the inflammatory signal to the brain, and the brain, via vagal secretion of acetylcholine (ACh) which binds α 7 nicotinic receptors on macrophages (α 7nAChR), suppresses peripheral cytokine production and guard against tissue damage [1,2]. The brain maintains immune homeostasis via in real time monitoring and adjusting the inflammatory response, and this regulation manner is quicker, effective and localized when compared to humoral ones. Activation of this “cholinergic reflex” has been found effective in various inflammatory disease such as sepsis, rheumatoid arthritis, Crohn’s disease, and cerebral and myocardial ischaemia. However, vagus nerve stimulation in humans is an invasive procedure and is not feasible under many circumstances. Pharmacological activation, such as nicotine, a non-specific α 7nAChR agonist, is associated with severe side effects and toxicity. Novel specific and effective targets activating CAP are still needed for the therapeutic interventions in inflammatory diseases.

MicroRNAs (miRNAs) are non-coding transcripts of 18-25 nucleotides, and they usually target mRNAs to modulate gene expression by 1.2 to 4.0 fold rather than acting as on-off switches for genes. miRNAs have been found to contribute to both neuronal and immune cell fate [3], but their involvement in the neuroimmune interface of CAP remains largely unknown. Several miRNAs assisting vagal cholinergic anti-inflammatory activity, named cholinomirs, has been identified only recently [2], especially miR-124 and miR-132. They are reported to be induced by LPS challenge and their treatment could potentiate the CAP and attenuate inflammation [4-6].

α 7nAChR is essential for the cholinergic anti-inflammatory action [2]. Downstream signal molecules that link α 7nAChR activation and pro-inflammatory cytokine production will be potential targets for therapeutic interventions that modulate inflammatory responses. MiR-124 is reported to be induced after LPS and α 7nAChR activation, which in turn targets signal transducer and activator of transcription 3 (STAT3) and TNF- α converting enzyme (TACE) and reduces IL-6 production and TNF- α release [4]. MiR-124 knockdown abolished the nicotine’s cholinergic anti-inflammatory action in LPS-triggered

macrophages and mice. Furthermore, miR-124 overexpression could significantly increase the survival rate of mice that were given a lethal dose of LPS [4]. Therefore, miR-124 might be a valuable target in treating sepsis. Moreover, miR-124 shows therapeutic potential in other inflammatory-related diseases. MiR-124 mediates the protective role of nicotine in DSS-induced mice colitis [7], and miR-124 reduction promoted inflammation and pathogenesis in ulcerative colitis patients [8]. Abnormal expression of miR-124 is also found in rheumatoid arthritis (RA) patients and ankylosing spondylitis (AS) patients. Forced expression of miR-124 repressed adjuvant-induced arthritis (AIA) in rats by decreasing synoviocyte proliferation, leukocyte infiltration, and cartilage or bone destruction through suppressing RANKL and NFATc1 [9-11]. MiR-124 overexpression suppresses experimental autoimmune encephalomyelitis (EAE) by deactivating microglia, a kind of macrophages resident in the brain and spinal cord, via the C/EBP- α -PU.1 pathway [12]. Microinjection of miR-124 into the peritoneum, which then be transported by macrophages to the site of spinal cord injury, could decrease the infiltration of macrophages and therefore ameliorate spinal cord injury [13]. MiR-124 also shows its therapeutic effect in the treatment of glioma, B-cell lymphomas and even liver cancers by regulating STAT3 or other targets [14-16]. Therefore, miR-124 is a promising candidate target for a broad spectrum of inflammatory diseases.

ACh is the neurotransmitter activating α 7nAChR in the CAP. It is hydrolyzed by acetylcholinesterase (AChE), therefore, AChE inhibition restricts inflammation by enhancing the cholinergic anti-inflammatory action. MiR-132 is the first miRNA that has been experimentally validated as targeting AChE. It can be induced by LPS exposure in leukocyte of both mice and human, which then targets AChE to attenuate inflammation. Transgenic mice overexpressing 3’UTR null AChE exhibited higher tissue AChE activity, excessive inflammatory mediators and impaired cholinergic anti-inflammatory regulation despite normal miR-132 levels [17]. MiR-132 also inhibits LPS-induced inflammation in alveolar macrophages by decreasing AChE level and enhancing cholinergic anti-inflammatory pathway [18]. Correspondingly, miR-132 modulates vagal tone and consequently inflammation in inflammatory diseases. MiR-132 levels are higher while cholinergic status and AChE activity were lower in inflammatory bowel disease (IBD) patients [19]. MiR-132 increases in RA patients as well [20]. Downregulation of miR-132 associates with EAE severity, and miR-132 mediates the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced anti-inflammation effect and attenuation of EAE [21]. During wound healing, miR-132 facilitates the transition from the inflammatory to the proliferative phase by regulating a large number of immune response- and cell cycle-related genes [22]. In viral or bacterial-infected cell/tissue, miR-132 is induced [23], which then inhibits both inflammatory cytokines and antiviral genes. Thus, miR-132 seems to be an attractive target for designing therapies aimed

to restore the cholinergic anti-inflammatory reflex in various inflammatory conditions [2]. Besides miR-132, miRNA-199a also suppresses cholinesterases to increase cholinergic signaling, resulting in decreased expression of proinflammatory cytokines [24]. Over 200 miRNAs are identified to target different cholinesterase transcripts, and most of them remain to be validated in the future [25].

In addition, MiR2055b is also reported to be involved in the cholinergic anti-inflammatory action. MiR2055b expression significantly increased following the activation of $\alpha 7$ nAChR in macrophages [26]. It is a critical mediator of cholinergic anti-inflammatory activity in late sepsis by targeting HMGB1, suggesting that it is also a potential therapeutic target for the treatment of inflammatory diseases.

The “micromanagement” of brain to immune system attracts special attention. MiR-124 and miR-132 has now been termed as “cholinomiRs”, which modulates both neuronal and immune processes and acts as negotiators between these two interacting compartments. There are other miRNAs (eg. miR-125b and miR-146a) involved in the neuroimmune interface which may also participate in the CAP [27]. By mimicking the activation of $\alpha 7$ nAChR or manipulation of AChE level, they could be beneficial for various pathological conditions, including inflammation, depression and anxiety, neurodegenerative diseases [2,28]. This editorial emphasizes the role of miRNAs in CAP and hopes to avail opportunity of using these “cholinomiRs” in the treatment of inflammatory diseases.

Financial and competing interests disclosure

This work was supported by grants from the National Natural Science Foundation of China (81273606 and 81473259 to XL, 81603116 to YS), and National Science and Technology Major Project (2014ZX09J14103-08C to XL). The authors declare no conflict of interests. No writing assistance was utilized in the production of this manuscript.

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