The regulatory region of the CHRFAM7A gene, the α7 nicotinic acetylcholine receptor subunit duplicate form involved in the cholinergic anti-inflammatory pathway

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It is well established that immune system can be no longer regarded as entirely autonomous in its regulation. Neuronal activities, by means of neurotransmitters' release, regulate the host's inflammatory response against pathogens infection and injury. Recent experimental evidences have suggested that the afferent component of the vagus nerve carries information about the inflammatory processes that occur at the peripheral level. The efferent fibres of the same nerve, releasing acetylcholine (ACh), reduce the level of pro-inflammatory cytokines (produced by innate immune cells) via a reflex mechanism called the 'Cholinergic anti-inflammatory pathway'[1]. Various studies have shown that the α7 nicotinic receptor (CHRNA7) is a key element for the functioning of this pathway.
Recently, CHRFAM7A gene was discovered[2]. It is the product of a recombination event that occurred in human where the portion of CHRNA7 gene, from exon 5 to 10, fused to a novel gene (FAM7A) which encodes four novel exons A, B, C from the serine/threonine kinase ULK4 gene, mapping to 3p22.1, and exon D of unknown provenance. CHRFAM7A gene is located on chromosome 15 (15q13-q14 region), 1.6 Mb apart from CHRNA7 gene, in the direction of the centromere, and in the opposite orientation with respect to CHRNA7.
Recently, our laboratory has shown that LPS treatment of a human leukaemic monocytic cell line (THP-1) down-regulated the expression of the CHRFAM7A gene, mainly by a transcriptional mechanism reliant on NF-κB[3]. This mechanism was confirmed in primary cultures of macrophages which unlike THP-1 express also CHRNA7. Treatment with LPS induces the expression of the CHRNA7 gene suggesting that in these cells CHRFAM7A may participate specifically in the innate immune system's inflammatory response and that heteromeric α7 receptors, consisting of both α7 subunit, could be formed.
These data suggest that the duplicated α7 subunit might act as a dominant negative regulator of the α7 nicotinic receptor, an hypothesis formulated independently by other laboratories, following electrophysiological recordings of Xenopus oocytes co-injected with CHRNA7 and CHRFAM7A mRNA[4, 5]. These experiments have shown that nicotine induced current decreases in proportion to the decline in the ratio of mRNA injected (α7 mRNA: mRNA α7dup) [4].
Many recent reports[6-8] have shown thatthe symptoms of chronic inflammatory disease, such as arthritis, inflammatory bowel disease and ulcerative colitis, can be alleviated by means of treatment with anti-TNFa antibodies or nicotine; however, treatments involving the neutralising of pro-inflammatory cytokines have been found to be inefficacious in the case of acute severe sepsis and toxic shock syndrome, thus indicating the continued need for anti-inflammatory therapies. This and the fact that trials of nicotine therapy have often been characterised by excessive side effects due to a lack of specificity for just one receptor type, underlines the importance of understanding the mechanisms of regulation of α7 and its duplicated isoform subunits in response to pro-inflammatory stimuli, to gain further insight into their role in the immune system and the cholinergic anti-inflammatory pathway, and greatly improve the discovery of anti-inflammatory treatments.
In order to study the role of CHRFAM7A in the 'Cholinergic anti-inflammatory pathway' we decided to isolate and characterize the CHRFAM7A 5' flanking region, which, to date, is unknown.

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