

## Tissue-Specific N-Terminal Isoforms from Overlapping Alternate Promoters of the Human AE2 Anion Exchanger Gene

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Abstract of:

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Previously, we isolated the human AE2 (SLC4A2) gene, a member of the sodium-independent anion exchanger family. Rat ortholog of this gene was reported to drive alternative transcription yielding N-terminal variants of the AE2a message. We thus analyzed the human AE2 gene in this regard. Using HepG2 cells, two alternative first exons, each splicing to exon 3 in alternative transcripts, were found to be transcribed from overlapping sequences of intron 2. Exon 1b1 corresponds to the rat variant "b"

and encodes three initial residues (MTQ) in AE2b1 isoform that replace the first 17 amino acids of AE2a protein, while the novel exon 1b2 encodes eight initial residues (MDFLLRPQ) in AE2b2 isoform. The relative abundance of AE2b1 and AE2b2 mRNAs was about 10% of AE2a mRNA each. Alternate promoter sequences have multiple potential binding motifs for liver-enriched factors, and dual-luciferase assays indicated that they possess the ability for driving transcription in transiently transfected HepG2 cells. Tissue survey showed that expression of human AE2b1 and AE2b2 transcripts is restricted to liver and kidney, while AE2a mRNA was encountered in all examined tissues. Our findings reveal a characteristic tissue-specific expression of two N-terminal variants of human AE2 from overlapping sequences

## Cytokine flow cytometry differentiates the clinical status of multiple sclerosis (MS) patients

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In this study we have examined intracellular cytokines in peripheral blood mononuclear cells (PBMC) of MS patients by flow cytometry (cytokine flow cytometry). MS progressive patients showed an increased number of cells producing interferon-gamma (IFN- $\gamma$ ) after activation with phorbol 12-myristate 13-acetate and ionomycin, compared with patients with clinically inactive forms ( $P < 0.001$ ) and with healthy controls ( $P = 0.001$ ). These cells belonged to the CD4<sup>+</sup> and CD8<sup>+</sup> subsets in similar proportions. Clinically inactive patients showed a lower level of cells producing IL-2 than controls ( $P = 0.03$ ) and active MS patients ( $P = 0.03$ ). Most IL-2-producing

cells were CD4<sup>+</sup> lymphocytes, although a small part of the IL-2 was also produced by CD8<sup>+</sup> cells. The percentage of cells producing simultaneously IL-2 and IFN- $\gamma$  was increased in active MS and they were mainly CD4<sup>+</sup> lymphocytes. No differences in the production of IL-4 were observed between groups. However, we found an increased IL-10 production in clinically active MS patients ( $P = 0.03$ ). Treatment with IFN- $\beta$  of active MS patients showed lower levels of cytokines when compared with untreated MS patients. This methodological approach could help in the follow up and therapeutic monitoring of MS patients.

**Keywords:** multiple sclerosis, intracellular cytokines, flow cytometry, interferon-beta

## Cerebral auditory plasticity and cochlear implants

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Previous animal research and clinical experiences in humans suggest the existence of an auditory critical period in language acquisition. We review the literature and present the changes within the cochlear nuclei in bilaterally deafferented adult non-human primates. We also present and analyse the results of 98 prelingually deaf children teenagers who underwent a cochlear implantation at the University of Navarra. Patients received a Nucleus 22 or 24 multichannel cochlear implant (CI). They were

grouped in five categories according to their age at surgery. Performance is compared with a control group of 58 postlinguals. Only early-implanted prelingual children (before 6 years of age) achieved a complete open-set speech recognition, even with better performance than postlinguals. These results clearly demonstrate the existence of a period of high neural auditory plasticity within the first 6 years of life. The introduction of auditory stimulation with a CI can not restore the loss of neural plasticity out of this period. Prelingual children under 6 years of age should receive a CI as soon as there is a reliable diagnosis of bilateral sensorineural hearing loss.