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2',5'-Oligoadenylate size is critical to protect RNase L against proteolytic cleavage in chronic fatigue syndrome.

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A dysregulation in the 2',5'-oligoadenylate (2-5A)-dependent RNase L antiviral pathway has been detected in peripheral blood mononuclear cells (PBMC) of chronic fatigue syndrome (CFS) patients, which is characterized by upregulated 2-5A synthetase and RNase L activities, as well as by the presence of a low molecular weight (LMW) 2-5A-binding protein of 37-kDa related to RNase L. This truncated protein has been shown to originate from proteolytic cleavage of the native 83-kDa RNase L by m-calpain and human leukocyte elastase (HLE). We investigated the possible role of 2-5A oligomers in the proteolytic action toward the endonuclease and show that incubation of CFS PBMC extracts with 2-5A trimer and tetramer, but not with the dimer, results in a significant protection of the native 83-kDa RNase L against cleavage by endogenous and purified proteases. Similar results are obtained with a purified recombinant RNase L. An analysis of the size of 2-5A oligomers produced by the catalytic activity of the 2-5A synthetase present in PBMC extracts further shows that samples containing the 37-kDa RNase L preferentially produce 2-5A dimers instead of higher oligomers. Taken together, our results indicate that homodimerization of RNase L by 2-5A oligomers higher than the dimer prevents its cleavage by proteolytic enzymes. The presence of the truncated 37-kDa RNase L in PBMC extracts is therefore likely to result, not only from the abnormal activation of inflammatory proteases, but also from a dysregulation in 2-5A synthetase induction or activation towards the preferential production of 2-5A dimers.