

Extract from a very good and complete website by **Cort Johnson**.

The original website is:

<http://www.phoenix-cfs.org/RNase%20L.htm>



A Channelopathy?

Englebienne, P., Herst, C. V., De Smet, K., D'Haese, A. and K. De Meirleir. 2001. Interactions Between RNase L Ankyrin-like Domain and ABC Transporters as a Possible Origin for Pain, Ion Transport, CNS and Immune Disorders of Chronic Fatigue Immune Dysfunction Syndrome. Journal of Chronic Fatigue Syndrome 8 (3/4): 83-102

(This was published prior to CFS ABA. Much of the information is found in CFS ABA. Some, however, is new).

The authors note that CFS patients exhibit many symptoms (including pain) that are characteristic of ion channel transport dysfunction. *(Ion channels occur in all membranes. They facilitate the transfer of ions and other substances into and out of the organelles in cells and of cells themselves.)* The potential for ion channel disruption in CFS patients was noted when it was determined that the RNase L's inhibitor (RLI), belonged to the ABC superfamily of ion channel transporters. RLI inactivates RNase L by binding to the 'ankyrin domain' section of the enzyme. The breakup of the ankyrin domain during the RNase L fragmentation seen in CFS patients suggested that these ankyrin fragments may be able to interact with and disrupt ion channel functioning. Ankyrins are proteins that (among other things) link the cells cytoskeleton to membrane proteins. They control the shape and elasticity of the cell membrane.

In order to determine which ABC transporters RLI was most similar to the authors made a 'sequence search' of a genetic database at the National Center for Biotechnology Information (NCBI) . Because ABC transporters typically interact with 'ankyrin domains' the authors sought to determine if RLI and other ABC transporters shared similar ankyrin interacting motifs. If they did then it would mean that the ankyrin motifs released during RNase L fragmentation could potentially interact with ABC transporters found in the cell.

Eleven ABC transporters with substantial homologies to RLI were

found. They shared with RLI an amino acid motif that allowed them to interact with ankyrins in the cells cytoplasm. Interestingly enough, given the high rate of chemical sensitivities found in people with CFS, several 'multidrug resistance transporters' involved in removing toxic materials from cells were found. These channels are also involved in the transport of choline and monoamine transporters. (*Both may be disrupted in CFS*). By disrupting glandular functioning in the epithelial tissues (skin, intestines, bronchii, etc.), one channel involved in chloride (Na) transport could cause night sweats and sarcoidosis (*a topic of recent interest*). Disruption of the SUR I channel could cause muscular weakness through losses of intracellular potassium. Another ABC transporter f(ABC3) plays an important role in the engulfment of apoptotic cells by macrophages. (*Might a dysfunctional engulfment process lead to elastase deposition in the cell? One wonders if this transporter is tied to antigen processing as well?*) The ABC7 protein transports heme from the mitochondria to the cytosol. ABC8 regulates macrophage cholesterol and is involved in tryptophan uptake. (*Some reports suggest tryptophan levels are increased in CFS.*) ABC8 dysfunction has been tied to several neurological diseases. TAP I is important in antigen processing and presentation by MHC I molecules.

The authors suggest fragmentation of the RNase L enzymes releases ankyrin fragments that have the potential to interfere with the function of several ABC transporters. They note that ABC transporter dysfunction could account for the following symptoms found in CFS patients: nightsweats, sarcoidosis, chemical hypersensitivities, macrophage dysfunction, immune deficiency, altered monoamine transport, increased pain sensitivity, Th2 dominance, CNS abnormalities, vision problems, potassium losses in muscles, transient hypoglycemia, depression (!).



Channelopathy Study

RNase L and Channelopathy

Nijs, J., Demanet, C., McGregor, N. R., Verhas, M., Englebienne, P. and K. De Meirleir. Monitoring a hypothetical in Chronic Fatigue Syndrome. Journal of Chronic Fatigue Syndrome

(The 'Belgian Research Group' (as I call them) responsible for most of the work on RNase L dysregulation is also in the forefront of attempts to characterize the different subtypes of CFS found. It has been apparent for several years that CFS can be invoked by different kinds of stressors (pathogens, toxins, psychological stress) and that the symptoms and the course of the disease can vary widely. The heterogeneous but still coherent patterns of symptom presentation and disease progression seen in CFS suggests that a central dysfunction capable of generating a wide variety of outcomes is present. The BRG believes that RNase L dysregulation with its myriad possibilities for immune dysfunction is that central dysfunction This paper is one in an apparently continuing series that seeks to define coherent subsets of CFS patients)

This study, while 'preliminary', is the first to look at ion levels in CFIDS patients and controls. The realization that RNase L fragmentation released ankyrin fragments with amino acid motifs able to interact with the ABC transporters that regulate ion flow in and out of the cells sparked concerns about a channelopathy in CFS (see [CFS ABA IV](#) and Channelopathy.) (*Channelopathies occur when cells exhibit ion imbalances. Because cellular activity is in part a function of the ion levels in cells, a channelopathy can disrupt cellular activity.*)

The researchers compared ion levels in CFS patients and controls. As so often occurs in CFIDS the results are mixed and may be confounded to some degree by the inadequacy of the current testing techniques. Fifty percent of CFS patients had abnormal whole body potassium content. In a display of heterogeneity that researchers must (with a sigh) expect from CFS patients, about 60% of the patients had high and 40% low whole body potassium levels. The authors note that because whole body potassium measures do not reveal potassium distribution patterns in the tissues or between intra and extracellular stores they are not sensitive enough to monitor discrete channelopathies. In an attempt to partially get around

this the authors calculated the ratio of serum (extracellular) to non-serum (intracellular) potassium. Because the ratio of serum potassium to non-serum potassium was higher than was expected they concluded that a channelopathy involving intracellular potassium loss was suggested in about half of CFS patients.

The SUR I channel controlling intracellular potassium levels seemed a likely candidate for malfunction in CFS patients. *(The SUR I (sulfonyleurea receptor) ATPase dependent K⁺ ion channel is of special interest because its activity is a function of ATP activity. Low levels of ATP cause the SUR I channel to open and release K⁺. Dysregulation of the SUR I channel typically causes severe muscle weakness (sound familiar?) because of severe K⁺ losses.)* The body attempts to rebalance ion distribution through increased aldosterone production (by the adrenal glands) which leads to increased tubular secretion. None of the CFS patients exhibited, however, the severe K⁺ losses typically associated with SUR I dysregulation. About 15% of CFIDS patients did exhibit, however, measures - low serum calcium levels and lower whole body potassium levels - suggesting that a similar scenario was occurring. *(Outflows of K result in increased calcium inflows into the cell. Lower serum calcium levels could suggest increased stores of intracellular calcium. The finding of reduced serum calcium (and probably therefore increased intracellular calcium) in these patients supports that authors suggestion that two calcium induced proteases, calpain and caspase 12, are respectively, agents of RNase L destruction and/or increased apoptosis in CFS.)*

A discriminant analysis involving percent fragmented RNase L, and immune cell (NK, T and B cells) and electrolyte levels revealed that reduced NK cell counts primarily differentiated CFIDS patients from controls. Reduced NK cells were strongly correlated with increased dominance of the 37-kDa RNase L fragment and decreased serum calcium levels. *(Since the 37-kDa fragment produces the ankyrin motifs believed to possibly disrupt ion channel functioning this finding appears (at least to this laymen) to buttress the authors theory linking RNase L dysregulation and a calcium channelopathy. This finding links, for the first time, two of the most consistently observed abnormalities in CFS; RNase L dysregulation and reduced NK cell counts. To bad NK cell activity was not measured.)* That reductions in serum calcium levels were not accompanied, as expected, by increased serum potassium levels, indicated once again, that nothing is simple in CFS. An expected association between increaseds levels extra-cellular potassium and activated T-cells was not found. The authors suggest, however, that the IL-1 increases seen in some CFIDS patients may be due to a

channelopathy.

Summation: the results regarding a channelopathy in CFS patients are mixed. The current technology is inadequate to fully explore a potassium channelopathy but some evidence indicates one may be present in a large subset of patients. A channelopathy involving RNase L dysregulation, decreased serum (and therefore increased intracellular) calcium levels may also be occurring in a subset of CFS patients. The authors suggest that a further exploration of the linkage between calcium homeostasis and RNase L dysregulation would be valuable.