Research on the mitochondrial proteome

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I am interested in elucidating the "meaning" hidden in the long, long strings of [actg] which comprise genomes. In recent years, the bulk of my research has involved close collaboration with others. Here I would like to mention some work with Kenichiro Imai and Michael M. Gromiha (both at CBRC) regarding the mitochondrial proteome.

For Christmas 2008, I wished for world peace, a full head of hair, and a 4 week vacation in Bali. Unfortunately, it appears that those will have to wait for another year, but Santa did bring a rather welcome gift -- a correspondence published in Cell.

In our correspondence we report the results of a proteome wide informatics analysis of a newly reported signal (the β-signal, Kutik et al.) for the integration of β-barrel proteins in the mitochondrial outer membrane. Our main result is the suggestion that mitochondria may have very few distinct types of such β-barrel proteins, perhaps 5-10 instead of the 100's of types which were once expected.

Those high estimates were based on the assumption that the mitochondrial proteome in general, and β-barrel proteins in particular, are similar to bacteria. An assumption based on the fact that mitochondria are thought to be the descendants of ancient bacteria, which somehow started to live inside the ancestor of Eukaryotic cells.

Hundreds of types of β-barrel proteins have been found in the outer membrane of bacteria. In some cases the structures have also been solved and several programs exist to classify unknown proteins as (bacterial) β-barrel proteins or not, based on their amino acid sequence. When applied to the yeast proteome, such programs suggested that mitochondria may also contain hundreds of β-barrel proteins -- but that work relied on the implicit assumption that programs trained on bacterial sequences could accurately predict mitochondrial β-barrels.

In contrast to such high estimates, the number of known types of mitochondrial β-barrel outer membrane proteins (MBOMPs), is only ***five***. We considered the discovery of the β-signal as an opportunity to reduce this gaps -- either by finding new candidate MBOMPs, or producing cirmcumstancial evidence to lower the the number of MBOMPs estimated to exist.

In a comprehsensive analysis of the known Eukaryotic proteome, using the β-signal and secondary structure prediction, we showed that, except for the known five kinds of MBOMPs, almost no proteins are promising MBOMP candidates. The one exception is a yeast protein called Uth1, which just may turn out to be the 6th MBOMP, although this is not at all certain at this point.

Another specific prediction we made, was that Mmm2, a known MBOMP, probably has a functional β-signal. This case is unique in that it is distal from the C-terminus, but this may be explained due to disorder in the region C-terminal to the putative β-signal site (See Fig.1).

I think this work truly represents "computational biology", and this type of correspondence represents a strategy for dry lab informaticians to have an impact on mainstream molecular biology.
Time will tell whether this was turns out to be a repeatable strategy for our lab...

References

1. "Dissecting membrane insertion of mitochondrial β-barrel proteins" S. Kutik, D. Stojanovski, et al., *Cell* **132**(6):1011-1024, 2008.
2. "Mitochondrial β-barrel Proteins, an Exclusive Club?" K. Imai, M.M. Gromiha, P. Horton, *Cell* **135**(7):1158-1159, 2008.

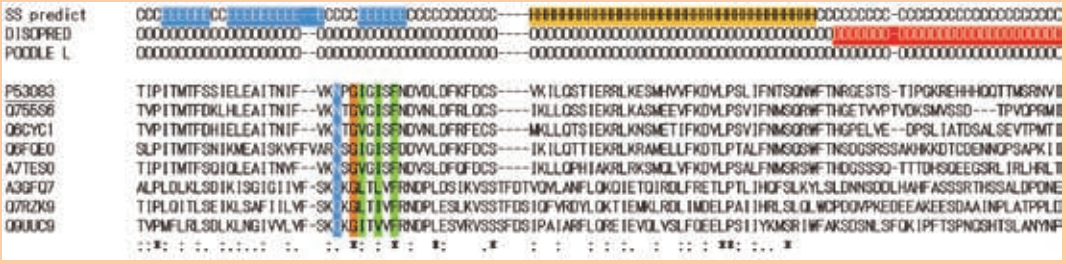

Fig.1 The putative β-signal region of Mmm2 and homologous proteins is shown in color. In the tracks over the sequence, E represents regions of predictedβ-secondary structure, and D represents predicted disordered regions.