Brain tissue repair in hereditary ataxia

Arnulf H. Koeppen, M.D.
VA Medical Center, Albany, N.Y.,
and Albany Medical College
The clinical course of the spinocerebellar ataxias (SCA) and Friedreich’s ataxia (FRDA) is variable. Age of onset and duration of illness range from short to very long. This variability can be attributed, in part, to the nature of the mutation, especially the “lengths of the CAG or GAA repeats”. This interpretation implies that brain and spinal cord atrophy proceeds at a different pace depending on the repeats. An alternate interpretation is that the central nervous system in some patients fails to repair the damage while in others it attempts restoration. What is the evidence for such repair?
Age of onset in FRDA vs. length of GAA repeats

![Graph showing the relationship between age of onset and GAA repeats in FRDA.](image)
<table>
<thead>
<tr>
<th>No.</th>
<th>Onset</th>
<th>Death</th>
<th>Allele 1</th>
<th>Allele 2</th>
<th>Area (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (C)</td>
<td>-</td>
<td>-</td>
<td>39</td>
<td>39</td>
<td>34.3</td>
</tr>
<tr>
<td>FRDA 1</td>
<td>32</td>
<td>87</td>
<td>234</td>
<td>126</td>
<td>22</td>
</tr>
<tr>
<td>FRDA 2</td>
<td>7</td>
<td>38</td>
<td>719</td>
<td>562</td>
<td>20.9</td>
</tr>
<tr>
<td>FRDA 3</td>
<td>16</td>
<td>49</td>
<td>492</td>
<td>366</td>
<td>26.3</td>
</tr>
<tr>
<td>FRDA 4</td>
<td>8</td>
<td>28</td>
<td>719</td>
<td>526</td>
<td>15.2</td>
</tr>
<tr>
<td>FRDA 5</td>
<td>30</td>
<td>75</td>
<td>637</td>
<td>234</td>
<td>25.2</td>
</tr>
</tbody>
</table>
Cross-sectional area of the thoracic spinal cord correlated with length of GAA repeats
The principal brain structures involved in ataxia
Microcircuitry in the cerebellar cortex

Climbing fibers from the inferior olivary nucleus

“Mossy” fibers from spinal cord and pons
Input from the pons

Cerebellar cortex

The pontocerebellar connections
Information processing in the cerebellum occurs by complex and highly coordinated transmission that includes excitation (glutamate) and inhibition (gamma-aminobutyric acid; GABA)
Input from the spinal cord

Output to thalamus and frontal lobe

cerebellar cortex

dentate nucleus

inferior olivary nucleus

Input from the spinal cord
“Key players” in the cerebellum and inferior olivary nucleus
Inferior olivary nucleus: A relentless monitor of Purkinje cell activity
Inferior olivary nucleus; neurofilament
Atrophic nerve cells in spinocerebellar ataxia (SCA)
SCA-6: neurofilament non-phosphorylated
SCA-2: Inferior olivary nucleus; neurofilament
Evidence of new growth of nerve cells and connections
Spiny branchlets arising directly from Purkinje cell body and primary dendrites
Climbing fibers seek and find new targets
VGLuT2 in normal cerebellar cortex
VGlut2 in SCA-6
“Grumose degeneration” of the dentate nucleus in SCA-3/MJD and Friedreich’s ataxia: Does it actually represent regeneration?
SCA-3/MJD: Dentate nucleus; Bielschowsky silver stain of nerve fibers
SCA-3/MJD: Dentate nucleus; neurofilament
Glutamic acid decarboxylase

A-B: Normal DN

C-E: DN in SCA-3/MJD
Conclusions

Current evidence supports some new growth of nerve fibers and migration of fibers to new sites. Sprouting is most apparent in cerebellar cortex and dentate nucleus. The functional importance of the process is not known, and it is unclear whether it is actually reparative. Nevertheless, an arrest of progressive degeneration and functional restoration by sprouting is a reasonable treatment goal.
Acknowledgments

Supported by Friedreich’s Ataxia Research Alliance, National Ataxia Foundation, Neurochemical Research, Inc., and Department of Veterans Affairs
Spare slides
In SCA-6, the inferior olivary nucleus survives because olivocerebellar (climbing) fibers find new targets
SCA-3/MJD: A disorder of the dentate nucleus
SCA-3/MJD; neurofilament, non-phosphorylated
Inferior olivary nucleus
SCA-3/MJD: Inferior olivary nucleus; neurofilament, non-phosphorylated
VGLuT2 as a marker of climbing fibers
Glutamic acid decarboxylase as a marker of corticonuclear connections in the dentate nucleus