Bif-1 and Autophagy

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- Goal: Investigating how neurons respond to injury and disease and trying to develop ways of mitigating or reversing neuronal dysfunction or death in injury and disease.

- Currently studying a protein related to two very important processes: apoptosis and autophagy

Apoptosis and Autophagy

- Apoptosis – programmed form of cell death
  - Too little: cells go on to survive and proliferate
  - Too much: associated with the loss of function in chronic human degenerative disease
- Autophagy - a process by which cells eliminate damaged proteins and organelles
  - Normal natural occurring homeostatic mechanism
  - Important for maintaining normal healthy neurons
  - If interrupted can activate neurodegeneration
  - Alteration (in both directions) in this process compromises neuronal function and viability

Bax-Interacting Factor 1 (Bif-1)

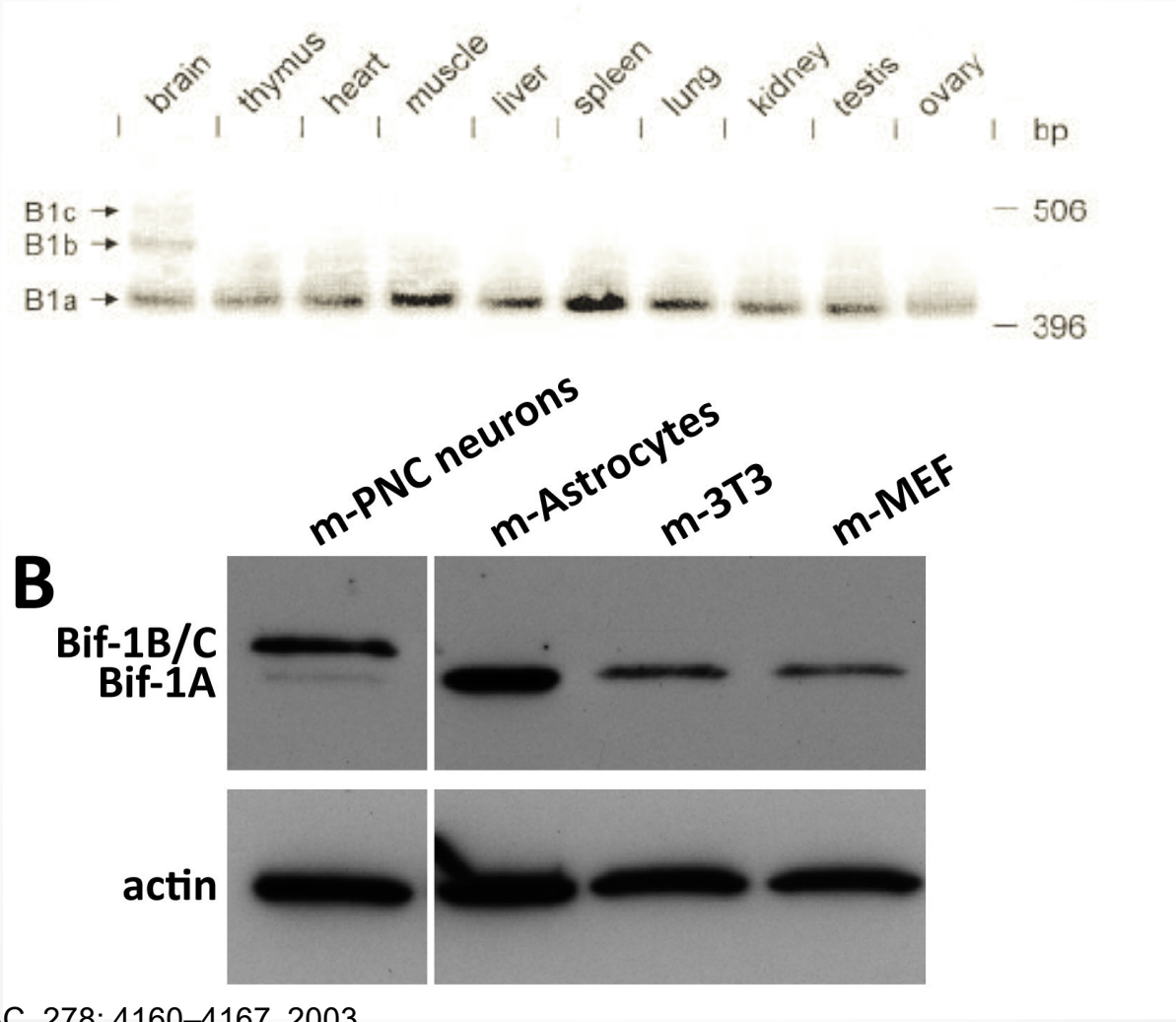
Regulator of apoptosis and autophagy

Binds to apoptosis promoter Bax

Loss of Bif-1 prevents Bax/Bak activation and apoptosis in non neuronal cells

Anti-apoptotic in nervous system: required to maintain healthy neurons

Bif-1 Neuron Specific Isoforms

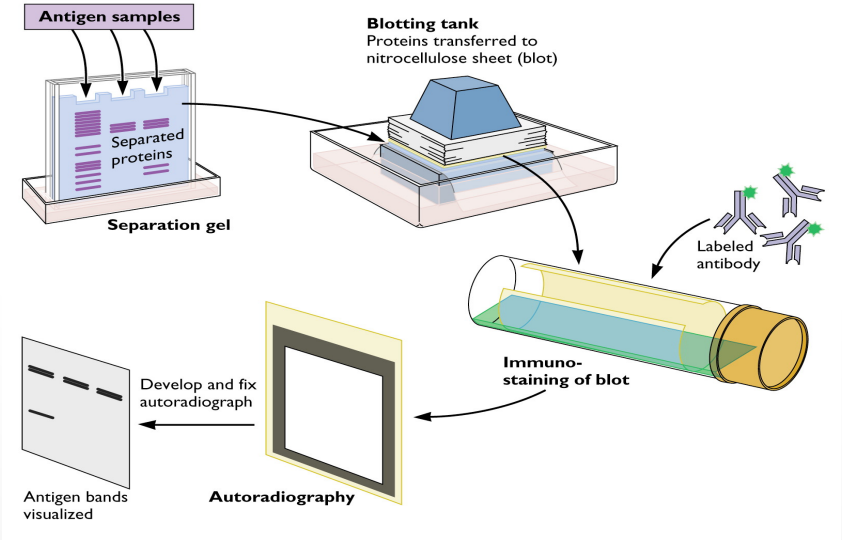


Modregger et al., JBC, 278: 4160–4167, 2003

Wang et al. The Journal of Neuroscience, 12 February 2014, 34(7): 2674-2683; doi: 10.1523/JNEUROSCI.4074-13.2014

Does Bif-1 play a role in the regulation of autophagy?

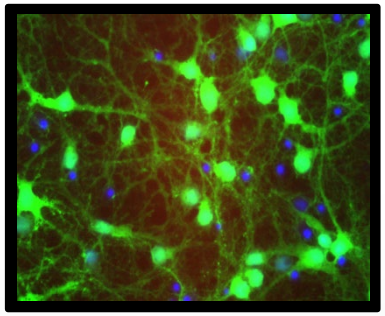
- Western Blot Analysis: Analytical technique used to detect and quantify proteins in a sample of tissue homogenate or extract (cultured neurons in our case)
  - Allows visualization of antibodies directed against each protein

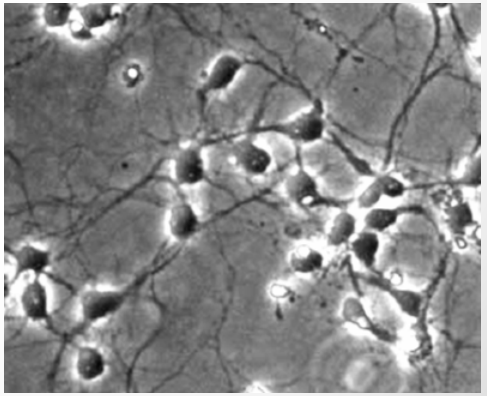


Racanello, Vincent. "Virology Toolbox: The Western Blot." *Virology RSS*. 7 July 2010. Web. 12 Aug. 2014.

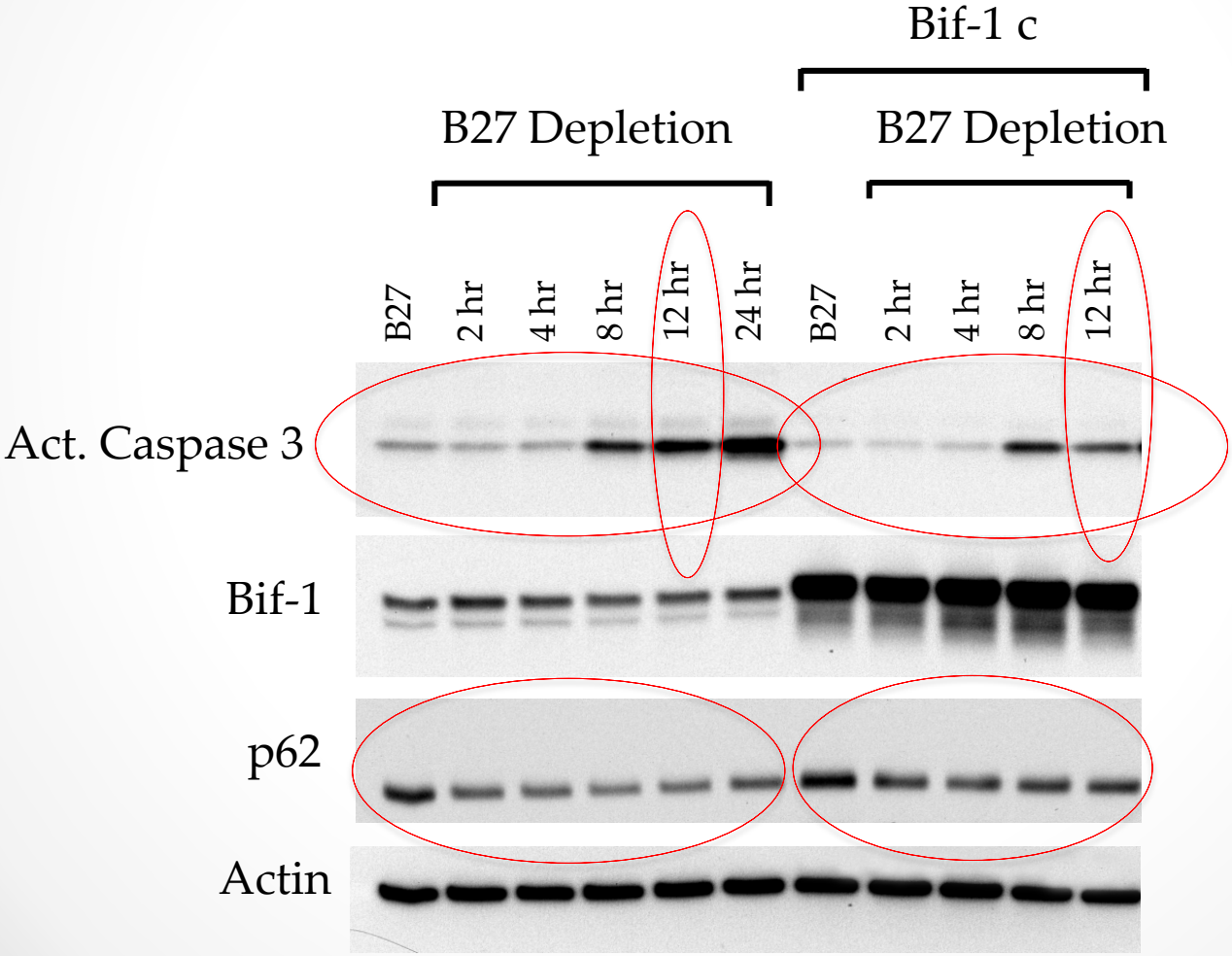
Our Model System

- (In vitro) Primary culture of newborn mice cortical neurons
- Induction of autophagy: B27 starvation
  - B27: Provides essential nutrients, trophic support and antioxidants for neuron survival
- Lentiviral transduction to manipulate levels of Bif-1 protein
  - Lentivirus used to upregulate or knock down gene expression
- Western Blotting
  - Apoptosis ↑ Activated Caspase 3 ↑
  - Autophagy ↑ p62 ↓





B27 Depletion-Induces Autophagy and Cell Death which is Reversed by Bif-1c Expression



Conclusions

- In contrast to what has been shown in non neuronal cells, in this neuronal model, Bif-1 seems to inhibit autophagy.
  - Dual Role? (depending on form of injury, disease or stress)
- Extend this in vitro work to physiological models of injury such as stroke
- Future Directions:
  - Mechanisms of Bif-1 action in autophagy
  - Therapeutic agent or treatment for people with neurodegenerative diseases

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