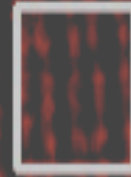


Muscle excitation-contraction coupling and the cell 'recycling' process

$l = 22.21 \mu\text{m}$, 2.4°



Myotubular Trust Family Conference

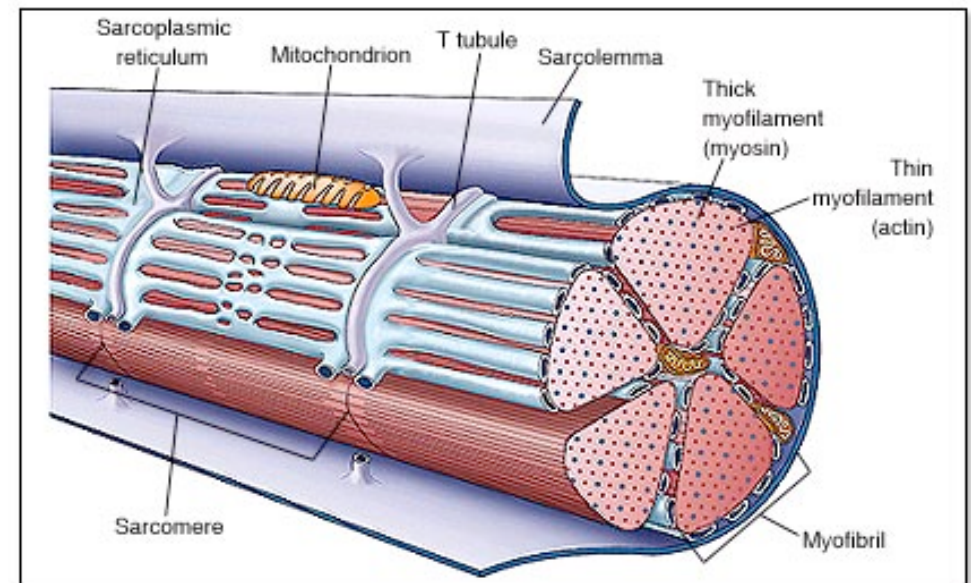
Prof. Susan Treves, Departments of Biomedicine and Anesthesia, Basl University Hospital,
Basel, Switzerland

London 12th July 2014

What is excitation contraction coupling?



- It is a mechanism that converts an **electrical signal** (depolarization of the plasma membrane), into **chemical signal** (an increase in the cytoplasmic free calcium concentration).
- In muscle it happens in a very specific region.
- Involves many proteins but the main players are **2 calcium channels**.
- One is called the **dihydropyridine receptor**. This is also a voltage sensor so it “feels” a change in membrane “charge”.
- The other is called **ryanodine receptor**



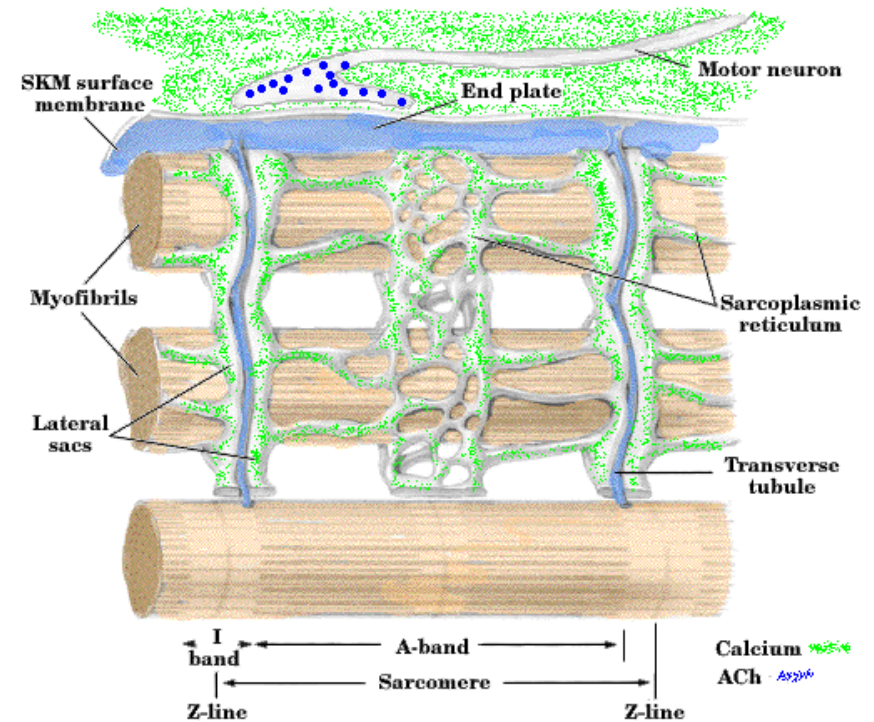
Why do cells use Calcium as a messenger?



The concentration inside the cell is different from that outside

K^+	139 mM
Na^+	12 mM
Cl^-	4 mM
Ca^{2+}	0.0001 mM

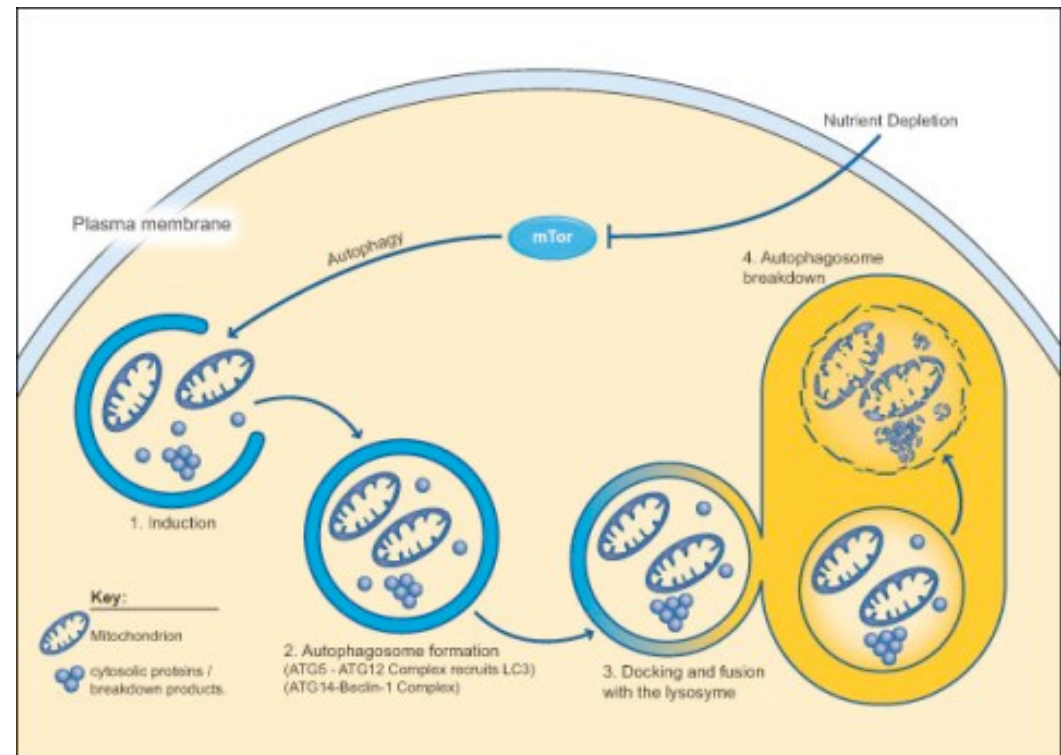
Universe	4 mM
	145 mM
	116 mM
	2 mM



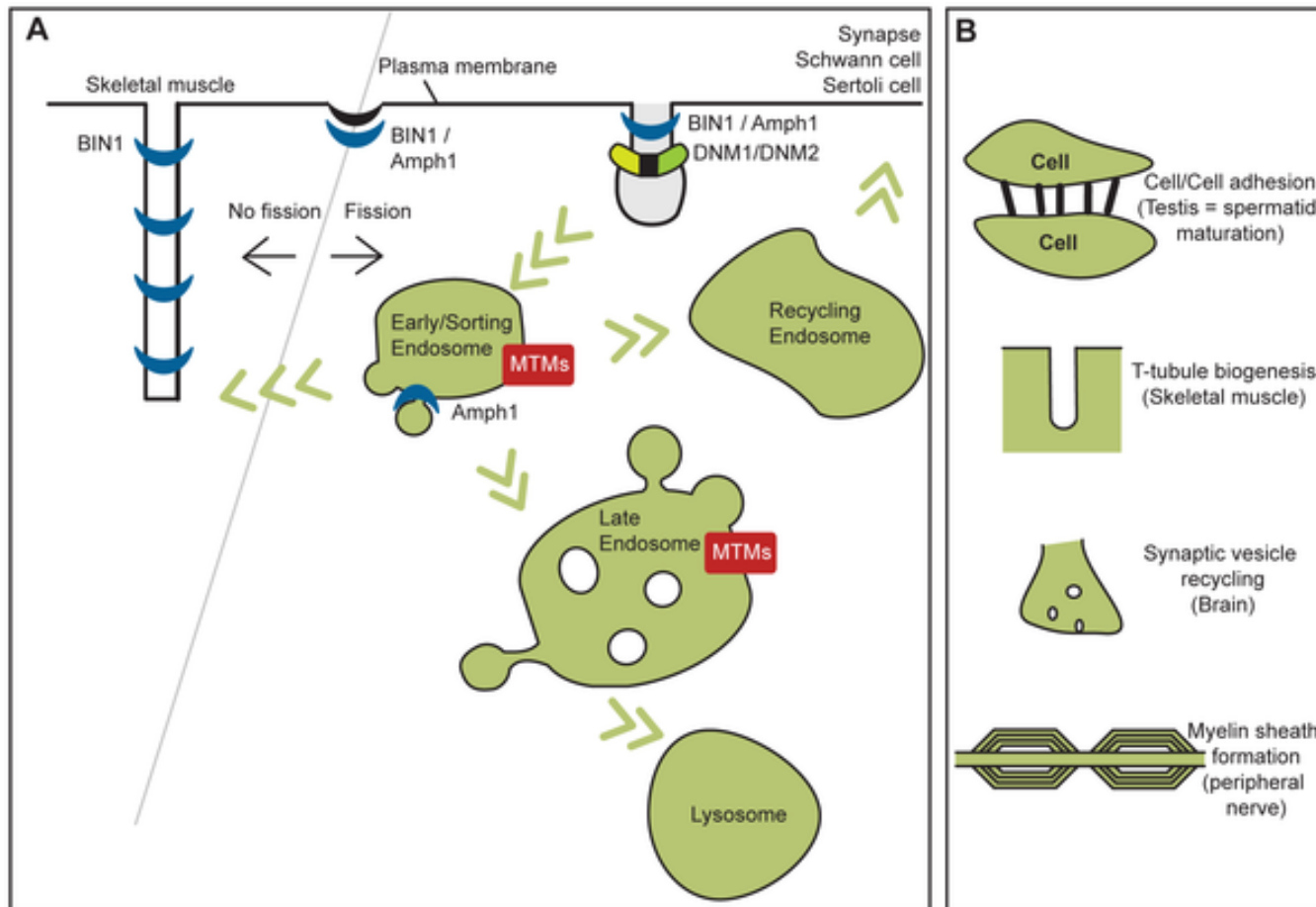
What is the recycling process?



- The recycling pathway is also called autophagy
- This means “self-eating”.
- It is process conserved throughout evolution.
- Proteins or organelles are degraded.
- It plays a fundamental role because it provides nutrients (during fasting or increased metabolic demands) and removes defective proteins or organelles.
- Involves trafficking of proteins inside the cell.



Most of the proteins implicated in CNMs play a role in membrane traffic.



- Protein (gene)**
- Myotubularins (*MTM*)
 - Amphiphsins (*BIN1*)
 - Dynamins (*DNM1/2*)

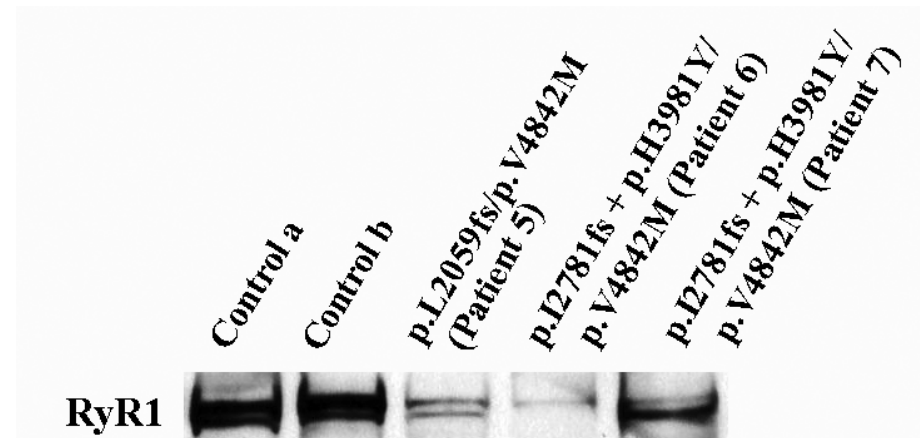
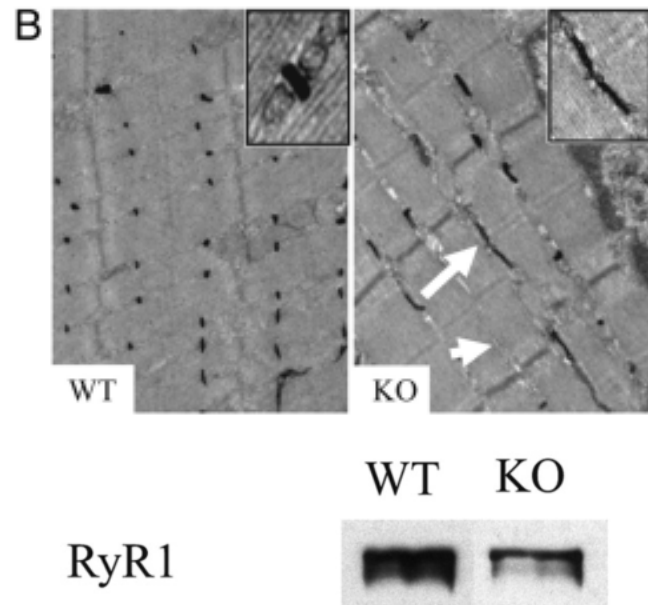
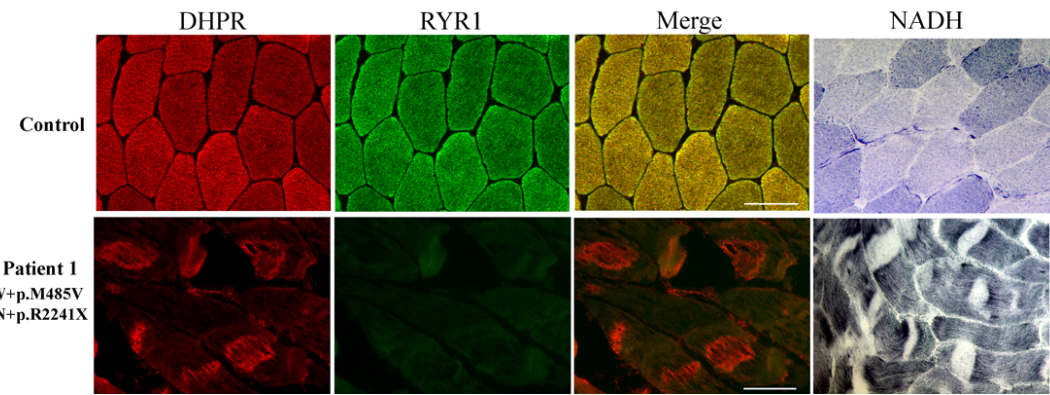
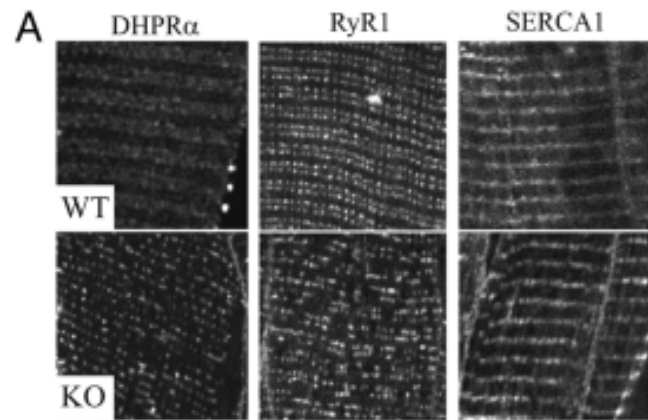
Is there a link between cell recycling and calcium?



- Membrane recycling depends on calcium.
- Patients with Centronuclear myopathy with *RYR1* mutations show a reduction in how much RyR1 protein is present in the muscle.
- Mice knocked out for *MTM1* exhibit membrane disorganization, accompanied by a decrease in expression of the 2 calcium channels DHPR and RyR1.
- Is the muscle weakness seen in patients with Centronuclear myopathy due to problems in excitation-contraction coupling?

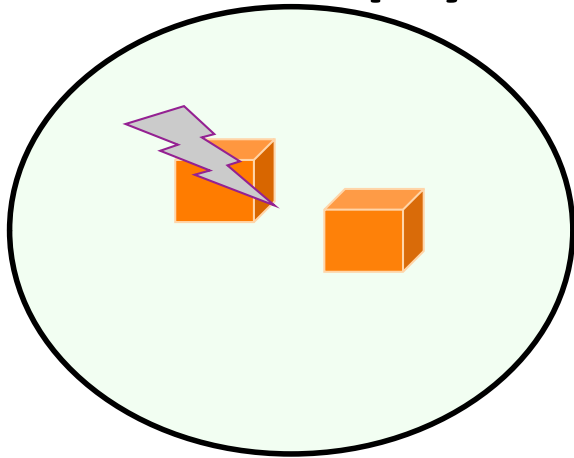


Similarities between experimental model and human disease

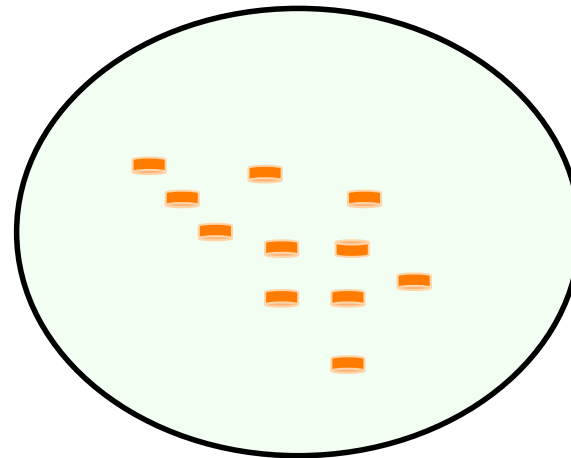


What do we do in the lab?

Small biopsy

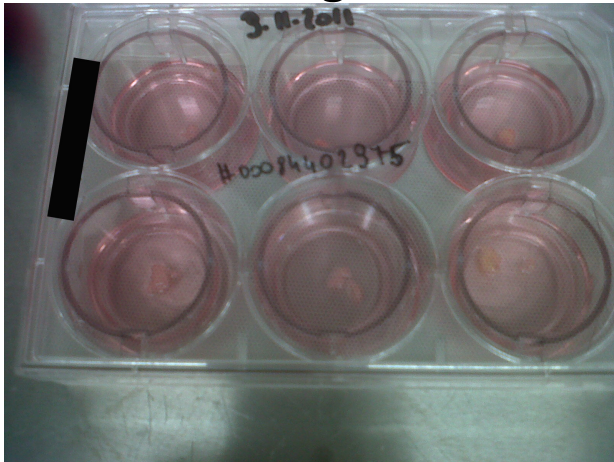


Cut into fragments (1-0.5 mm)

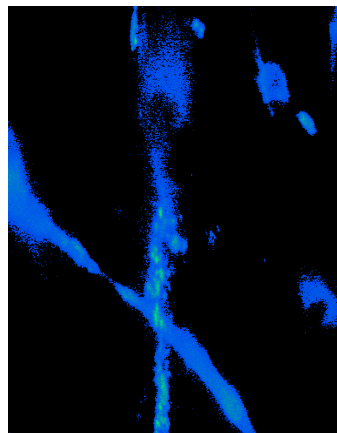


Place biopsy in multi-well plate

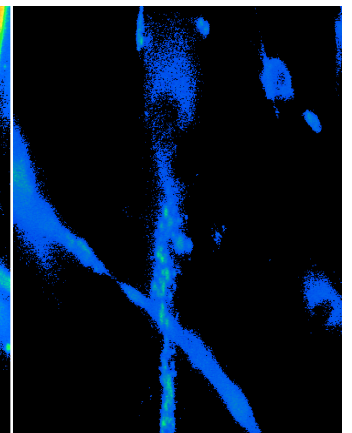
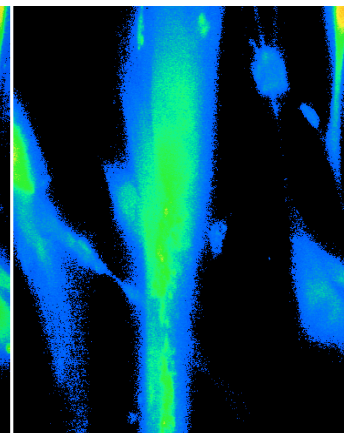
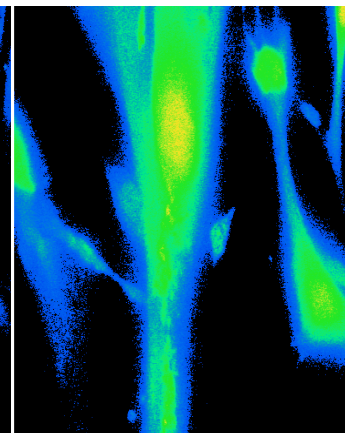
Satellite cells grow into insert



Myoblasts into flask



Differentiated myotubes



What we have found so far....

