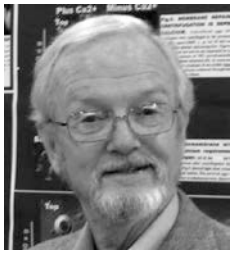
特別講演２

Discovering the cause of adult-onset muscular dystrophy by electron microscopy of mouse genetic models.



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We have discovered that there is a system of muscles in the external ear or 'pinna' of the common laboratory mouse, muscles that are particularly suitable for electron microscopy (EM), as they are thin and flat, and they lie immediately under the skin, and they are attached to the stiff cartilage of the ear, so they are not disturbed during LM-observation nor fixation for EM.
In the course of other studies on the metabolism of *other* tissues in the mouse ear, we also discovered quite by surprise that these ear-muscles are acutely sensitive to cold, indeed they *degenerate completely* when mice are exposed to a wintery environment. This raised the possibility of using this new ear-muscle prep to study muscular dystrophy, which we have begun to do, and which has already shown us that mouse ear muscles in at least the Miyoshi-type (limb-girdle muscular dystrophy type 2B) are distinctly *hypersensitive* to cold. This further allowed us to obtain optimal EM-images of the very first structural abnormalities that appear in these muscles, as they are *just starting* to degenerate in the cold. These are easily recognizable as *dislocations* in the normally orderly registration of adjacent myofilament-bundles or 'myofibrils'. Additionally, we used these ear-muscles to develop a new method for selectively visualizing the critical excitatory-apparatus of all muscles, the T-tubules, (namely, by staining them selectively with a colloid of uranium-tannate). This further allowed us to show that the observed cold-induced myofibrillar-dislocations *sever or break* T-tubules, which makes the dislocations *accumulate* and get much worse, leading finally to muscle degeneration! Furthermore, since we could show that the protein that is mutated in Miyoshi muscular dystrophy (namely dysferlin, which is thought to be involved in membrane healing) is normally located on these T-tubules but is *missing* in the disease), we can conclude that the Miyoshi disease in humans is caused by a *failure to heal or re-anneal* breaks in T-tubules caused by the normal wear-and-tear of everyday life (which was only exacerbated or exaggerated by our cold-experiments). We suspect that a similar scenario exists for several of the *other* adult-onset muscular dystrophies (especially for LGMD-1C, where the mutation is in caveolin, a T-tubule-related protein), and we are certain that our new ear-muscle-prep and our new method for stressing muscles by exposing them to cold will continue to provide tremendous insights for researchers studying the electron microscopy of all sorts of muscle disease.