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DESTRUCTION ET RÉGÉNÉRATION DES FIBRES MUSCULAIRES

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Translation in English

DESTRUCTION AND REGENERATION OF MUSCLE FIBERS

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It is likely that muscle damage is extremely frequent: muscle fibers are indeed very fragile. At rest, they have the consistency of a jelly and break at the slightest touch, as the physiologist who tries to isolate them knows very well. In contraction, they are subjected to enormous mechanical stresses, particularly during eccentric movements. But, although very frequent, these muscular lesions are of little consequence. The subject only experiences some muscle pain and aches. Even surgical aggressions seem to traumatize the muscles much less than the other organs, a happy circumstance which gives the surgeon a lot of freedom, leading him to consider the muscles as a fabric with impunity to be cut. This robustness of the muscle is explained by an enormous power of regeneration based on a rapid proliferation of stem cells, the "satellite cells". They reconstitute the destroyed muscle fibers by a process close to their embryogenesis.

The initial lesion remains obscure. It probably begins with a rupture of a few myofibrils under mechanical stress of external origin to the fiber, for example, a stretching force by the contraction of an antagonistic muscle. This lesion is much localized, affecting only a few microns of a fiber several centimeters long. The ruptured ends retract and pull the plasma membrane, which in turn ruptures. The micromolecules (ions, enzymes) of the sarcoplasm spread in the interstitial spaces and can gain blood. One of the most abundant and active enzymes is creatine phosphokinase (CPK). This explains the rise in this enzyme in the plasma regularly observed after exercise, even relatively moderate. The connective tube, the "sarcolemma", which surrounds the muscle fiber resists mechanical traction. The broken ends of the myofibrils retract each time this fiber is excited, so that the lesion lengthens, perhaps several millimeters, but the fiber remains contained in the sarcolemma tube. The very abundant calcium ions in the interstitial fluid can diffuse almost freely through the injured membrane and will activate intracellular Ca-dependent proteolytic enzymes. In the hours following the lesion, the pycnosis damages the nucleus, then the mitochondria swell, lose their crests and dissolve, the Z lines dissociate, the myosin fragments while the actin resists. This phase is intrinsic degeneration. In one or two days, the injured area is invaded by polymorphonuclear neutrophils and macrophages. They cross the sarcolemma tube and phagocyte the cellular remains: this phase is extrinsic degeneration. Meanwhile the satellite cells are activated. These cells are very small spindle cells a few microns long snuggled against the membrane of the muscle fiber inside the sarcolemma tube. They are quite numerous, about 2 or 3 per millimeter of fiber length. The lesion activates them by an unknown mechanism to enter into proliferation. The cycle of successive divisions is rapid, with a period of around twenty hours. The newly formed cells remain confined in the segment of the sarcolemma tube cleaned and abandoned by the macrophages. They pair end to end and fuse into long multi-nucleated cells, the myotubes. Protein synthesis is accelerating: sarcomeres organized into myofibrils appear around the nuclei. The myotubes laterally merge and join the still functional ends of the parent muscle fiber, to which they will soon merge. The nuclei remain central for some time, the last trace of regeneration, then finally migrate to the periphery. The regeneration is then complete. Nothing remains of the lesion, and functional recovery is complete. The complete lesion-degeneration-degeneration cycle lasted less than 8 to 10 days.

It must however be recognized that in many points the above statement leaves something to be desired. Indeed, a circumscribed muscular lesion is very difficult to find experimentally and its mechanical effect can be masked by compensatory recruitment of other muscle fibers. *In vitro*, an obvious macroscopic mechanical effect can be observed without the histological lesion being found. In fact, most of our information is drawn from experimental models where large muscular disturbances are caused: artificial ischemia, focal lesions by physical aggression (burns, frostbite, sections) or chemical (myotoxic: local anesthetics, venoms of snakes), transpositions or free grafts of muscles, grafts of fine muscles. In all these cases, additional lesions are introduced to the muscular lesions proper: some more or less known

as stopping circulation, enervation, rupture of the sarcolemma tubes, others with unknown effects, such as the action of toxins on the activity of satellite cells.

We cannot begin here a discussion of all these factors, but we wish to discuss at least one point, concerning the above assertion that regeneration is functionally total. In fact, the only argument for this statement follows from the initial hypothesis: if our muscle fibers are really so fragile that a large number of them are constantly destroyed and regenerated, especially during intense exercises, we are forced to admit that regeneration must be complete since training and exercise improve muscle performance. However, a muscle grafted from one mouse to another follows the degeneration-regeneration cycle, but the maximum isometric force hardly reaches more than 80% of the control muscle. We therefore conclude that in this case, the regeneration is not complete. We have recently observed that the transplanted and regenerated soleus muscle contracts more quickly than the control muscle, a phenomenon explained by the appearance of new forms of myosin. Although the maximum strength of the regenerated soleus is less than the control muscle, its maximum mechanical power is identical. From this point of view, regeneration is therefore complete. We therefore see that the concept must be qualified: a muscle can recover completely after injury certain parameters, but not others. It is therefore not excluded that even a small lesion changes the characteristics of a muscle fiber.

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