A quest into muscle plasticity

The Laboratory for Muscle Plasticity is constantly exploring and researching in its quest to perfect muscle function

Soft tissues (muscle, tendon and ligaments) demonstrate a graded capacity to respond to the impact of external stimuli with molecular and cellular adjustments that improve their capacity to withstand the original impact. The diagnostic assessment of the adaptive potential of muscles provides indications on how bottlenecks in the current therapy of musculoskeletal defects can be overcome. The aim being to innovate surgical and rehabilitative approaches to permit the handicapped individual to maximise adaptive stimuli and processes.

Muscle health is an economic factor

Plasticity is described as the ability of an organism to change its phenotype in response to changes in the environment. This has its place in body homeostasis, especially regarding the implication of skeletal muscle in bodily actions. Through its mechanical actions in locomotion, posture and speech, muscle facilitates interactions with the environment and affects energy expenditure. The reduction of muscles' functional ability thus develops an important negative impact on our human capacity.

Muscle weakness and associated poor fatigue resistance is a major challenge to modern Western society. It arises due to a reduction in the force-producing capacity of skeletal muscle with prolonged inactivity (disuse), injury or disease. The consequent reduction in strength negatively affects physical fitness and mobility, which lowers the quality of life. Based on epidemiological evidence it is estimated that associated costs accrue to CHF 2,000 (~€1,906) per person per year (Fig. 1). Musculoskeletal health is thus an important financial substrate in Western society.

Our research focus

The strategic aim of the Laboratory for Muscle Plasticity at Balgrist University Hospital is to expose the molecular and cellular mechanisms underpinning muscle affections in clinical situations ranging from simple exertion-induced soreness to major musculoskeletal disease of striated muscle, and more so their reversion with rehabilitation. This is done within the goal to identify biological bottlenecks, which opens venues for novel interventions that can halt muscle deconditioning and degeneration. Specific emphasis is put on the myocellular processes of rehabilitative and therapeutic measures after orthopaedic surgery. Towards this end we focus on patient groups which could benefit from an improvement in muscle function. Further, we assess transfer effects on musculoskeletal health and quality of life.

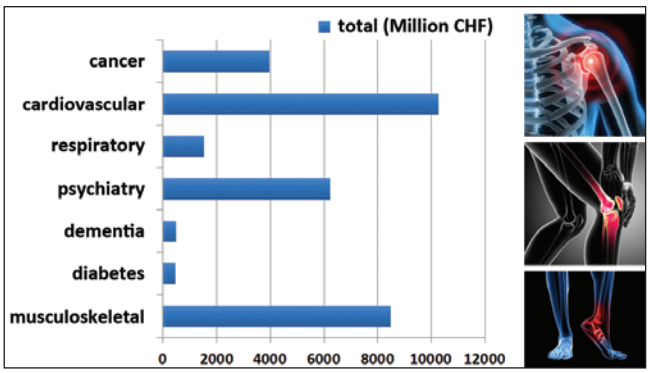

Fig. 1 Healthcare cost in 2011 of the seven major non-transmissive diseases. To the right: focus on affliction of the musculoskeletal system

Research approach and strategy

The Laboratory for Muscle Plasticity at Balgrist deploys state-of-the-art methodology to optimise surgical approaches and rehabilitation based on genetic and physical constitution. The research is embedded in the Orthopaedic Hospital of the University of Zurich. By 2016 it will extend its patient-tailored biomedical research by integrating its activities in the musculoskeletal research centre at Balgrist campus. The following sections highlight active areas and the scientific background of our research towards a personalised approach to musculoskeletal health.

Background

Skeletal muscle function relies on shortening of the embedded muscle cells (fibres) and this depends on bioenergetic processes. This results in the capacity for force production, which is dictated by the composition and anatomy of skeletal muscle. This especially implicates the volume content of slow and fast contractile types of myofibrils, mitochondria and capillaries. These cellular variables define the maximal force (strength) and fatigue resistance of contraction. Both features are conditioned in a pulsatile manner by muscle use. This occurs because there is a natural degradation of muscle material due to wear and tear of cellular structures. The wasted muscle material must be replaced through the activation of biosynthesis. Mechanical stress with weight-bearing contractions is a potent stimulus for the activation of these synthetic pathways. Energy flux is its most important modulator. The specific conditioning of muscle through physiological factors is amply illustrated by the different outcome of strength-type *versus* endurance-type sports activities that involve a high load or high repetition number of contractions, respectively.

The underlying regulation involves the activation of a molecular programme that is embedded in our genes and which dictates the proteins to be made, i.e. expressed. The study of gene expression allows exposing the mechanistic relationship between the dose and duration of exercise and the resulting effect on muscle function. This knowledge is important to develop rehabilitative

interventions or define stimuli that produce a functional outcome. Therapeutic measures based on information of muscle plasticity would thus offer considerable socioeconomic potential for musculoskeletal medicine, but its application in the management of healthcare is underdeveloped today.

Repair mechanisms after rupture of the anterior cruciate ligament

As a joint, the knee exerts the important task of translating and potentialising forces being produced in the upper, large thigh muscles via the lever arm of the femoro-patellar articulation. This function is essential to counteract the forces of gravity through the extension of the knee. On the downside, however, the knee joint is exposed to particularly high rates of mechanical stress. This may damage anatomical structures that stabilise the knee joint if the resulting mechanical strain exceeds the typical safety factor for musculoskeletal tissues.

This is especially true for the mechanical impact on ligaments that operate in the lateral direction, such as the anterior cruciate ligament (ACL) and medial patella-femoral ligament. Their integrity is challenged by biomechanical vectors that operate in transverse directions to the main movement of the knee joint. This often occurs with intense physical activity in sports and during manual labour and may lead to tendon rupture. This is a relatively frequent condition affecting one in 1,750 individuals each year. Because it renders the function of the affected knees unstable, repair of the damaged soft tissue is strongly indicated. This requires orthopaedic surgery and subsequent physical procedures to support the functional recovery of the reattached ligament and connected muscle as it is weakened due to the prior injury and enhanced catabolism during unloading. Typically this is initiated by resistive types of exercise. The dose-effect relationships for musculoskeletal adaptations with rehabilitation, which define the therapeutic success of orthopaedic surgery, are not well defined.

Towards this end we pursue an investigation to define the time course of molecular and cellular adaptations in a major knee extensor muscle with exercise-based rehabilitation subsequent to surgical repair of the ruptured ACL. This study is inspired by our results showing that eccentric types of endurance activity, such as that seen with downhill sports activities (skiing), represent a potent intervention to strengthen the musculotendinous structures that operate on the knee joint. We expect that our study will provide important information as to the quality and effect size of the rehabilitation for the deconditioned muscle and knee function.

Focus on rotator cuff disease

The rotator cuff is a complex group of skeletal muscles which facilitate shoulder function. This involves important actions such as internal and external rotation as well as the abduction of the arm.

Full or partial tears of rotator cuff tendons are a relatively frequent condition affecting a considerable portion of the population. Ageing-associated factors and injury represent the major cases of the disease. Thereby current numbers indicate that 40% of subjects above 60 years of age demonstrate tears of the rotator cuff. This severely complicates daily activities as it renders the accentuation of the upper extremity in one or more direction hard to impossible. If left untreated, shoulder function is permanently affected because the detached muscle degenerates by shrinkage

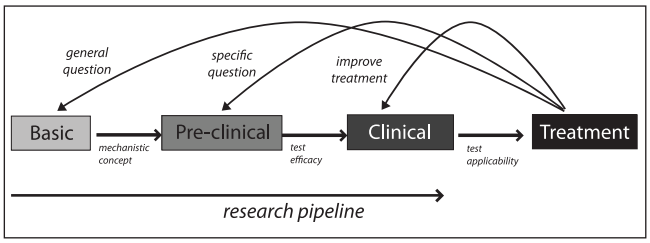

Fig. 2 Research approach scheme of the conceptual path of the research strategy of our integrated studies towards improved treatment of the orthopaedic patient

of muscle cells and their conversion into fat tissue. Eventually this limits kinematics of respective joints, which has the ultimate consequence in the degeneration of the glenohumeral joint. At this point no other option remains than to surgically replace the joint with an expensive endoprosthesis to reinstate limb function. Surgical interventions aimed at repairing the affected shoulder muscle involve the reattachment of the ruptured tendon to the bone via an anchor. Thereby the prevention of adipogenic and atrophic processes in the detached muscle is a priority to warrant optimal surgical repair of the ruptured muscle-tendon unit.

Towards improving the therapy of rotator cuff disease, we investigate the time course of molecular and cellular alterations in animal models of the ruptured rotator cuff. The aim is to map the mechano-regulated pathobiological process and risk factors of muscle degeneration, which contributes to the healing of muscle-tendon complex. Specific emphasis is put on testing the effectiveness of pharmacological compounds targeting the degradation of structural anchors of the contractile apparatus in muscle fibres.

The knowledge is integrated in a clinical trial in which we characterise morphological and genetic biomarkers of the healing response of rotator cuff muscle after surgical repair of the detached tendon. This is motivated by the reported contribution of heritable factors to the healing of the reattached rotator cuff. The aim is to reintegrate the gathered knowledge into personalised surgical approaches and therapies that more efficiently prevent detractions in shoulder muscle function in critical responder groups (Fig. 2).

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