Editorial

Current Perspectives on Muscle Regeneration and Diseases

Skeletal musculature plays a crucial role in locomotor activity, postural behaviour and breathing, thus the maintenance of a working musculature is fundamental for animal survival: for this reason the mechanisms involved in muscular regeneration processes have been widely investigated. Skeletal muscle can be damaged not only by direct trauma (such as intensive physical activities or lacerations) but also by neurological dysfunction or innate genetic defects. In the last years several studies have been addressed to find out new therapeutic strategies to recover some of the pathological conditions associated with poor muscle regenerative capacity, such as in myogenic dystrophies. For a long time mammalian animal models have been considered the best model for studying muscle regeneration and for dissecting a human disease. However, during the last decade a lot of evidence has shown that the mechanisms controlling muscle development and regeneration have been highly conserved. This fact encouraged researcher to employ invertebrate models to identify and characterize the different population of cells involved in the regenerative process and the molecular pathways which finely orchestrate the activation of these set of cells during the repair process.

These collected reviews contribute to the current knowledge about muscle biology and pathology and the potential of different therapeutic strategies (drug, gene, cell-based therapies) to promote muscle regeneration using both vertebrate and invertebrate models.

The paper by Ciciliot and Schiaffino [1] contains different aspects about muscle regeneration. Firstly they review the three phases that are involved in regeneration of mammalian skeletal muscle and underline the role of nerve activity in this phenomenon. The occurrence of the regeneration process is then discussed in a chronic degenerative setting, i.e. muscular dystrophies, and in relation to traumatic injuries common in sport medicine. A final description of the age-dependent decline in muscle regeneration potential leads to a discussion of the molecular factors underlying muscle growth that could thus be recruited to boost regeneration and rescue muscle loss in aging muscle and muscular dystrophies.

Formigli and collaborators [2] review the current knowledge about the use of skeletal myoblasts for cardiac regeneration. Although the use of these cells for a therapeutic purpose has always been controversial, the possibility to genetically engineer them to potentiate their paracrine attitude and their function versus cardiac regeneration appears now attracting and is raising great expectations. To this purpose, the Authors focus on key aspects underlying the interactions between skeletal myoblasts and the host cardiac tissues, with a particular attention towards the cell-derived factors that are involved in cardiac repair and regeneration.

The high conservation of mechanisms that control muscle development and repair has led to the establishment of some invertebrate models of human muscular disorders.

In this context, Daczewska *et al*. [3] compare the cellular and molecular events underlying muscle development and regeneration in normal and pathological conditions in *Drosophila*, a classical model system which is amenable to global genomic/transcriptomic approaches, genetic manipulation and high throughput chemical compound screening.

The extensive similarities in the myogenic pathways between fruit fly and vertebrates provide a powerful platform for the identification of candidate genes and to test their potential to rescue mutant phenotypes.

The paper by García-Arrarás and Dolmatov [4] emphasizes the use of a less conventional animal model, echinoderms, for studies on muscle regeneration. These animals show amazing regenerative capabilities and, due to their close phylogenetic relation to vertebrates, can surely represent interesting model systems to determine cellular and molecular processes involved in muscle regeneration and to set up pharmacological studies for muscular diseases.

In contrast to what previously thought, skeletal muscle satellite cells are not the only source of myogenic precursors in skeletal muscles. In their paper, Tamaki and colleagues [5] provide data about skeletal muscle-derived stem cells, with a particular attention to two stem cell populations previously identified in their lab, that are able to differentiate into myogenic-vasculogenic cells in the interstitial spaces of murine skeletal muscle. The Authors discuss not only the possible physiological role of these cell *in vivo* but also their contribution to muscular regeneration and use for the treatment of severely damaged muscle.

The paper by Grimaldi *et al*. [6] emphasizes the use of an unusual invertebrate, the leech *Hirudo medicinalis*, as a new emerging model for studying endothelial and hematopoietic precursor cells involved in muscle post-natal growth and regeneration processes. Moreover, the Authors propose a new "*in vivo* cell sorting method" to isolate a specific population of hematopoietic/endothelial precursors cells which can differentiate in muscle.

Muscular dystrophies are a heterogeneous group of diseases affecting both children and adults which lead to progressive loss of muscle strength and mass in patients. The review by Lamperti and Moggio [7] focuses on the clinical features and genetic classification of Congenital

Muscular Dystrophies, dystrophinopathies and Limb Girdle Muscular Dystrophies. In addition a survey of three main strategies to develop a therapy (i.e. gene, cell and drug therapy) is presented.

Among the strategies to treat Duchenne Muscular Dystrophy, exon skipping has emerged as one of the most promising and has recently undergone completion of Phase I clinical trials in humans. In their paper Wilton and Fletcher [8], starting from an overview of the history of splice intervention therapy, focus on the pre-clinical antisense oligomer splice-switching studies and the ongoing clinical trials to by-pass disease causing dystrophin mutations. They also discuss commercial/ethical issues and future perspectives related to this strategy.

Type 1 diabetes is an autoimmune disorder characterized by absence of insulin. The absolute dependence of patients on exogenous insulin for survival has boost research towards the search for new therapies and among them the use of gene therapy is of wide interest. In their paper, Mann *et al*. [9] focus attention towards the muscle, a target tissue that is not only amenable to gene therapy technology, but its central role in whole body metabolism and glucose homeostasis makes it a good candidate for treatment of diabetes, through its modification in order to produce and secrete insulin into the blood and/or increase muscle glucose uptake.

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