CALL FOR PAPERS | Mechanisms of Tissue Repair

Unraveling the basic principles

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HOW DO TISSUES RESPOND TO injury? The call for papers “Mechanisms of Tissue Repair” was launched to stimulate the search for novel answers to this intriguing question. This special call received the attention of scientists from various disciplines, and it is worth revisiting the contributions which have appeared on this topic in the American Journal of Physiology–Regulatory, Integrative and Comparative Physiology over the past few years.

Tissue integrity is threatened for various reasons, including mechanical, inflammatory, chemical, and ischemic injury. One common theme that has evolved is that regeneration in many tissues recapitulates the events during normal development. For example, regeneration in the skeletal muscle stimulates the expression of embryonic and neonatal myosin heavy chains before the appearance of the fast adult isoforms (1, 6). Likewise, tissue repair after myocardial infarction mimics an embryonic program with reexpression of genes normally associated with cardiac development (17). Deciphering the molecular mechanisms of normal development may therefore advance our knowledge of tissue regeneration in the postnatal organism.

Several articles related to tissue repair in the skeletal muscle system addressed the role of nerve activity and calcineurin. Calcineurin is a calcium-calmodulin-activated serine-threonine phosphatase, which is highly correlated with skeletal muscle mass (22). It promotes slow fiber-type gene expression in the regenerating muscle by dephosphorylation of transcription factors such as nuclear factor of activated T cells and myocyte enhancer factor 2 (13, 27). Furthermore, calcineurin and PKB [also known as Akt (PKB/Akt)] are involved in tissue remodeling during recovery from disuse muscle atrophy (23). Recent observations suggest that the transitory increase in calcineurin phosphatase activity in regenerating skeletal muscle results from slow motor neuron activity (7, 15, 18). However, in one of these studies it was shown that a slow phenotype could be triggered and maintained in regenerating skeletal muscle in a calcineurin and nerve-independent manner (7). Thus innervation and calcineurin phosphatase activity are not the only regulators of slow myosin heavy chain expression in skeletal muscle.

Important hints to other relevant factors can be obtained with the use of microarray technology for gene expression profiling in the regenerating skeletal muscle. Taking this approach, Flück et al. (3) revealed major, biphasic patterns of gene expression with increasing mechanical load of atrophied skeletal muscle (3). Remarkably, transcript levels of molecules involved in protein synthesis and proteasomal mRNAs were increased after 1 day of reloading and correlated with the number of muscle fibers surrounded by the extracellular matrix protein tenascin-C (2, 3). On the other hand, expression of fatty acid transporters, respiratory chain constituents, and voltage-gated cation channels was transiently reduced, depending on the number of damaged fibers, and the regain in muscle weight (3). These findings indicated that the transcriptional response to mechanical reloading of atrophic skeletal muscle is related to the processes involved in mechanical damage and regeneration of muscle fibers. Importantly, the capacity to regenerate after physical injury is not restricted to healthy skeletal muscle but was also reported from the dystrophic diaphragm of mice (mdx) with lack of dystrophin (9). Mdx mice served as a model for Duchenne muscular dystrophy (DMD), as they harbor a nonsense point mutation in exon 23 of the dystrophin gene (20). These results raise the hope that the regenerative capacity residing within dystrophic muscles may eventually become exploitable for future therapeutic purposes (9). It should be recalled in this context that the recovery of skeletal muscle fiber function from injury is also dependent on monocyte/macrophage invasion (24) and the proliferation of satellite cells (11). Satellite cells are myogenic precursors, which are located between the basal lamina and plasmalemma of mature muscle fibers and have been implicated in the replacement and/or repair of damaged fibers after traumatic injury (21).

Recent findings indicate that the sarcolemmal Na⁺/K⁺-pump could be a potential target for improving force recovery after muscle cell damage. Thus it was shown that stimulation of the Na⁺/K⁺-pump either with the β₂-adrenergic agonist salbutamol or epinephrine increased force recovery by 40–90% in a model of fatiguing rat skeletal muscle (10). Both spontaneous and salbutamol-induced force recovery were prevented by ouabain (10). Membrane depolarization due to influx of Na⁺ and Ca²⁺ ions is a common mechanism in fatiguing rat skeletal muscle (4). Salbutamol treatment repolarized the membrane potential to a level measured in unfatigued muscle but failed to restore normal Na⁺ and K⁺ content (10). Thus restitution of the contractile force with salbutamol likely reflects improved excitability of the skeletal muscle.

Two other studies addressed the function of specific cell types in different models of tissue repair. Keloids are abnormal fibrous growths of the dermis that can develop after wounding. Using serum stimulation to mimic some aspects of the wound

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microenvironment, cultured keloid fibroblasts but not normal fibroblasts responded with enhanced formation of the profibrotic transforming growth factor (TGF)-β2 (28). Increased expression of TGF-β2 in the keloid fibroblasts appeared to be mediated by the p38 MAPK pathway (28). These results suggested that keloid formation relies—to some extent—on inherent differences in how fibroblasts respond to wounding (28).

To compare the restitution of native colon epithelia with that of cultured colon-derived cell lines, single-cell lesions were induced in mouse colonic surface epithelia by iontophoretic injection of Ca2+ (5). Tissue repair, which was assessed by the means of confocal laser scanning microscopy and electrophysiological techniques, was considerably faster in native colon epithelia than in cultured cells. Furthermore, proinflammatory cytokines and pathogenic bacteria delayed the restitution (5). These observations, which could become relevant with regard to inflammatory bowel disease, point to a key role of very small lesions at the onset of pathogenic processes in the intestine.

Owing to its high susceptibility to ischemic/hypoxic injury, the kidney has recently been used for exploring the mechanisms of tissue repair (8, 12, 14, 25, 29). Ischemic acute renal failure is a disorder with high morbidity and mortality (16). It comprises a regeneration phase, whose molecular basis is still unclear. Novel insights into the mechanisms of renal tissue repair may come from studies analyzing the distribution patterns and expression levels of nephrogenic proteins in posts ischemic rat kidneys. Remarkably, a variety of embryonic genes were reexpressed in rat kidneys after ischemia/reperfusion injury (26). Expression of these nephrogenic proteins occurred in a characteristic manner beginning with mesenchymal factors at the initial reparation phase followed by tubular and vascular endothelial markers (26). It appears therefore likely that morphogenesis in the developing kidney and restoration of mature kidney function after ischemic renal injury is established through a similar genetic program. Recent findings indicate that partial renal ischemia elicits a heterogeneous efferent protein expression in developing kidney (26). It appears therefore likely that morphogenesis in the developing kidney and restoration of mature kidney function after ischemic renal injury is established through a similar genetic program. Recent findings indicate that partial renal ischemia elicits a heterogeneous efferent protein expression in developing kidney (26). It appears therefore likely that morphogenesis in the developing kidney and restoration of mature kidney function after ischemic renal injury is established through a similar genetic program. Recent findings indicate that partial renal ischemia elicits a heterogeneous efferent protein expression in developing kidney (26).

REFERENCES


