Signal Transduction and Gene Expression in Striated Muscles: A Symposium

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The adaptability of skeletal muscle in response to contractile activity is now well recognized, based in large measure on the pioneering work of exercise and muscle physiologists in the 1960s and 1970s (Gollnick and Ianuzzo, 1972; Holloszy, 1967; Salmons and Vrbová, 1969). These studies as well as others laid the foundation for a plethora of investigations on the plasticity of muscle, employing a multitude of experimental approaches, and several excellent compilations of the literature have appeared (Booth and Baldwin, 1996; Pette, 1980; Pette and Vrbová, 1992; Saltin and Gollnick, 1983; Vandenbergh, 1987; Williams and Neufer, 1996). Summaries devoted to specific topics, such as the adaptability of contractile proteins (Pette and Staron, 1997) as well as the energy supply of the contracting muscle cell (Essig, 1996; Hood et al., 1994), have also been published.

A common thread throughout this literature is the lack of understanding of the molecular basis governing the adaptations that take place. Some plausible signals have been suggested (Booth, 1988), and these currently form the basis for working hypotheses. In addition, the initial physiological event that triggers subsequent signaling cascades is not established. Muscle tension development, cell stretch, or electrical activity could potentially be involved in activating a series of intracellular reactions (i.e., phosphorylation-dephosphorylation, upregulation of transcription factors), which will control the transcription of specific genes. While work in this area is progressing (see Aronson et al., 1997; Bassel-Duby et al., 1994; Michel et al., 1994), much can also be learned about phenotypic adaptations from an appreciation of the large number of studies devoted to transcriptional regulation during muscle development and regeneration (Chambers and McDermott, 1996; Olson and Klein, 1994; Olson et al, 1995). In these areas, a common regulatory theme is the control of gene expression. Similar mechanisms are likely utilized to activate overlapping gene expression programs as a muscle cell develops, adapts

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to altered function, and regenerates after damage. Two families of transcription factors have been studied extensively during muscle development with respect to how they activate muscle genes: the basic Helix-Loop-Helix myogenic genes (MyoD family) and the Myocyte Enhancer Factor 2 (MEF2) gene family (McDermott et al., 1993; Olson et al., 1995; Weintraub, 1993). Whether these and other transcription factors are involved in muscle adaptation will receive intensive scrutiny and could yield important insights into the molecular mechanisms that regulate phenotypic adaptations in muscle.

In addition to studies on muscle-specific transcription factors that promote muscle development, investigations on the neuromuscular junction have been particularly informative with respect to the dynamic nature of muscle fibers. This synapse has been used for many years as a model system for studying the interaction of nerve-evoked muscle contractile activity as well as neurally derived trophic factors that regulate muscle gene expression (Duclert and Changeux, 1995; Fambrough, 1979; Merlie and Smith, 1986). The acetylcholine receptor on the postsynaptic membrane represents an abundant protein that displays remarkable plasticity in response to alterations in physiological conditions, such as denervation and contractile activity (Chahine et al., 1992; Goldman et al., 1985). As summarized in this symposium by Jasmin et al. (1998) and Goldman and Sapru (1998), recent work has expanded our knowledge to other synapse-specific proteins, such as acetylcholinesterase and utrophin. Researchers have begun to investigate the transcription factors involved in the regulation of the expression of these and other synapse-specific proteins during altered physiological states.

The molecular etiology of cardiac hypertrophy is another highly visible area of work. This adaptive growth response, clearly apparent in individuals suffering from chronic pressure- or volume-overload situations, is a dominant health concern, particularly as the heart progresses from a compensated state to one in which compromised contractile function occurs. Recently, a number of novel experimental models have been developed to investigate cardiac gene expression and hypertrophy using isolated cardiac myocytes. These include electrical stimulation of myocytes (Xia et al., 1997) as well as the stretching of cells on a silicone substrate (Sadoshima et al., 1992; Sadoshima and Izumo, 1997). Results from these studies have shed light on early signaling events that lead to the hypertrophic phenotype. In addition, traditional models of experimental hypertrophy, such as aortic constriction (Nishio et al., 1995) and the induction of myocardial infarction (Tsoporis et al., 1997), continue to be essential to determining the underlying events involved in the hypertrophy process. The paper in this symposium by Parker et al. (1998) and the presentation made by S. Izumo highlight some of the early molecular events during cardiac hypertrophy and define important signaling pathways involved in the process.

References


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