

Human cytomegalovirus IE1 promoter/enhancer drives variable gene expression in all fiber types in transgenic mouse skeletal muscle

ABSTRACT

The CMV IE1 promoter/enhancer is not restricted to specific types of fibers, but it can still drive germ-line transgene expression. This is important because not all fiber varieties express the same gene at high levels due to regional differences in overall expression levels and within-fiber-type variability. Given the multinucleate syncytial nature of muscle fiber regions, it is unlikely that this variability is caused by variegating heterochromatinization. The soleus muscle, however, would be suitable for experimental gene driven by CNVX1 elements.

INTRODUCTION

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A recent study (2) using mouse fibroblasts from the mouse line Iba1 (C. elegans) has suggested that the protein Iba1 is a promoter of Iba1-related genes that are involved in collagen synthesis and remodeling, and thus could be used in the development of new tissues. We have recently demonstrated that human IE1 is a transcription factor that is required for the expression of several genes involved in the development of skeletal muscle fibroblasts.

The human IE1 gene is expressed in several tissues, including muscle, connective tissue, and bone. The IE1 gene also is The expression of experimental germ-line transgenes in skeletal muscle can be altered through genetic manipulation, which requires knowledge of the specific promoter/enhancer elements present in different fiber types. The four primary fiber types in rodent limbs and axial muscles are slow-contracting (type I) and fast-contracting (Type IIA, IIB, and IIX, also known as IID), which vary in activity patterns and have distinct metabolic and myosin heavy chain characteristics. Each of the four principal fiber type expresses a distinct gene that determines fast or slow contractile speed, while several other muscle protein gene families contain members that are differentially expressed in fast and slow fibers. Studies have begun to characterize the genetic disorders controlling mechanisms. The emergence of "universal" viral promoters, such as the cytomegalovirus (CMV) IE1 promoter, is intriguing due to their potential for broad, high-level expression. However, the transcriptional specialization of the various fiber types raises the possibility of fiber-restricted or differential expression in skeletal muscle. While CMV IE1-driven expression has been observed in several transgenic mouse studies, Baskar et al have found significant differences among skeletons and other tissue based on this mechanism. We demonstrate that CMV/LacZ, a type of CAMP, is not restricted solely to the fibers of the hindlimb, and that histological analysis of transgenic mice with the CAV -galactosidase construct revealed that its expression is highly variable within all the major fiber types.

CONCLUSION

Although the CMV IE1 promoter/enhancer is not restricted to specific types of fibers, it can drive germ-line transgene expression in all major skeletal muscle fiber types. The cause of the marked within-fiber-type variability is uncertain, as regional effects on expression levels have been

observed. It is also possible that within-versus-and genetic material for-purpose (IEC) heterochromatin would not lead to “wide-scale” differences in physiological status among some muscle groups