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Invited Review

Skeletal muscle fibre types: detection methods and embryonic determinants

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Summary. Muscle fibres used to be simply classified as either type I, IIa or IIb. Advances in molecular and histological techniques have, however, lead to the realisation that the phenotypes of muscles are more varied than this. An additional fibre type (IIX/IID) has been discovered, fibres with intermediate fibre types have been described and there is accumulating evidence that the fibres types described from the study of limb muscles are not necessarily applicable to other skeletal muscles, such as the jaw and extra-ocular muscles. Further to this has been the discovery that diversity occurs at all stages of muscle development. There are subpopulations of myoblasts and myotubes as well as various types of muscle fibres. The relationships between the different stages of development is still under study. However, it is clear that each stage of muscle development is influenced to a certain degree by prior events. Consequently, the characteristics of mature fibres reflect both their developmental origins and influences from the adult environment, such as their patterns of muscle activation.

Key words: Myoblast, Myosin heavy chain, Myotube, Immunohistochemistry

Introduction

The generation of a wide range of active muscle force is a prime function of skeletal muscle. Animals have adapted to environmental demands by developing specialised fibres with a diverse range of anatomical, biochemical and physiological properties. Interest in this diversity extends from physiology into pathology as the various specialised fibres can be differentially affected in various diseases.

The heterogeneity of muscle fibres has been traditionally attributed to the fact that different fibres have different patterns of activation (reviews: Buchthal and Schmalbruch, 1980; McLennan, 1990b). However, this cannot account for all the variability. In this paper, we will review the histological classification of muscle fibres before proceeding to discuss whether the embryological origins of muscle fibres affect their mature characteristics. We will focus entirely on studies of vertebrates as the characteristics of invertebrate muscles fibres have recently been reviewed (Paniagua et al., 1996).

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Older methods of classification

The classification of muscle fibres is usually based on their speed of shortening although the metabolic characteristics of a fibre can also be taken to account (reviews: Landon, 1982; Pette and Staron, 1997). The ATPase activity of a myosin is the major determinant of the speed of contraction of a fibre: fast and slow fibres contain isoforms of myosin which, respectively, have higher and lower ATPase activity (Barany, 1967; review: Schiaffino and Reggiani, 1994). With the simplest forms of ATPase histochemistry, fast contracting fibres stain more darkly than slower contracting fibres because of their greater enzymatic activity, but the simplest form is rarely used as it does not discriminate between the subtypes of fast fibres.

ATPase histochemistry is more powerful when the procedure includes a step that differentially inactivates myosin isoforms. Acid pre-incubation is the classical way of achieving this. Slow myosin is acid stable and after an acid pre-incubation the slow contracting fibres (Type I) stain more darkly than the fast contracting fibres (Type II). By varying the pH of the incubation, the type II fibres can be further subdivided into type IIA, IIB and IIC (Brooke and Kaiser, 1970; Guth and Samaha, 1970). There are numerous variations to these procedures (Gollnick et al., 1983; Matoba and Gollnick, 1984; Gardiner and Olha, 1987) but none of them are widely used and the results obtained with the different procedures are not always comparable (Dahl and Roald, 1991 and see the discussion of IIX fibres below).

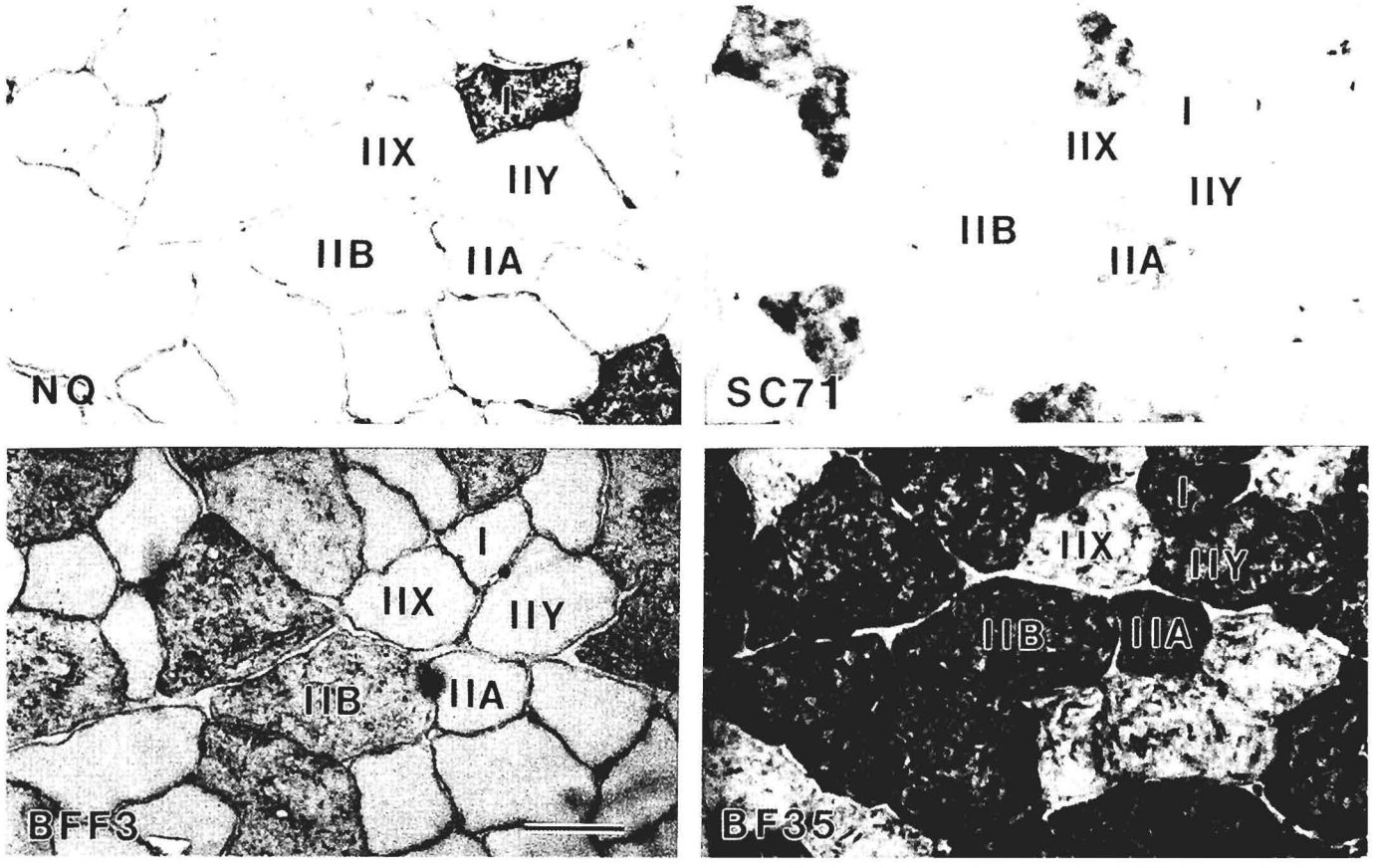
The use of ATPase histochemistry is still common, particularly within clinical settings, but it is now known

to be a crude and limited technique. Increasingly, fibre typing is being done using antibodies which discriminate between the various isoforms of myosin. Such studies have revealed new fibre types and also demonstrated that some fibres are intermediate between two fibre types. That is, a fibre can express two isoforms of myosin (LaFramboise et al., 1991; DeNardi et al., 1993; Zardini and Parry, 1994). Furthermore, immunohistochemical fibre typing is very reliable and fully comparable between laboratories whereas ATPase histochemistry is sensitive to minor variations in procedure.

Immunohistochemical fibre types

Antibodies used for fibre typing are directed against the heavy chain of myosin (MHC) (Fig. 1). Four major isoforms have been identified: MHC I/β is a slow isoform found in skeletal and ventricular muscles (Yamauchi-Takihara et al., 1989) whereas IIa, IIb and IIx (IId) are fast isoforms. The fibres classified as IIC by histochemistry contain a mixture of myosin isoforms (Billeter et al., 1980; Termin et al., 1989). Consequently, there is no IIc MHC.

IIX fibres were discovered through the use of a panel of antibodies (Schiaffino et al., 1985, 1989; Baer and Pette, 1988; Hämäläinen and Pette, 1993) with their existence being definitively proven by the demonstration that IIx MHC is produced from a gene which is distinct from those encoding IIa and IIb MHCs (DeNardi et al., 1993). IIX fibres are indistinguishable from IIB fibres with the standard acid-preincubation/ATPase histochemistry but have the appearance of type IIA fibres in formaldehyde-alkali/ATPase histochemistry (Schiaffino et al., 1989; Larsson et al., 1991). The level of glycolytic



	I	2A	2B	2X	2Y
NOQ	■	□	□	□	□
SC71	□	■	□	□	□
BFF3	□	□	■	□	□
BF35	■	■	■	□	■

Fig.1. Identification of fibre types by immunohistochemistry. Four adjacent sections of an adult rat EDL muscle were stained with anti-MHC monoclonal antibodies reactive with MHC I/ß (NOQ), MHC IIa (SC71), MHC IIb (BFF) and all MHCs except MHC IIx (BF35). The fibre marked with IIY has characteristics which are distinct from type I, IIA, IIB or IIX fibres. The myosin content of the IIY fibres is unknown. Bar: 400μm.

enzymes in IIX fibres is intermediate between that of IIA and IIB fibres (Larsson et al., 1991) whereas the speed of contraction of IIX fibres is intermediate between type I and IIB fibres (Schiaffino et al., 1989).

The number of distinct fibre types is undefined, but certainly much larger than the four major types discussed above. For instance, the jaw muscles of some species contain a distinct form of MHC, which is called superfast due to its very high level of ATPase activity (Hoh and Hughes, 1988) and the ocular muscles contain α cardiac MHC (Rushbrook et al., 1994).

Myosin isoforms in developing muscles

Immature muscles contain two MHC isoforms which are referred to as embryonic and neonatal MHC. The embryonic and neonatal MHC genes have an evolutionary relationship to IIa, IIb and IIx MHC genes (Weydert et al., 1985; Soussi-Yanicostas et al., 1993) and are therefore considered to belong to the family of fast myosins. These developmental isoforms are not expressed in mature limb muscles, except in extraocular muscles (Periasamy et al., 1985; Jullian et al., 1995). Conversely, there is little or no expression of either IIa, IIb or IIx MHC during the early stages of muscle development (LaFramboise et al., 1991).

The situation with the slow myosins is less clear. Myotubes express a slow MHC (Narusawa et al., 1987) but there is now doubt about whether the slow MHC is I/β MHC or a developmental isoform which is closely related to I/β MHC (Hughes et al., 1993). In the case of aves, the existence of developmental isoforms of slow myosin have been clearly established (Crow and Stockdale, 1986a; Page et al., 1992; Nikovits et al., 1996).

The presence of the developmental isoforms of MHC in developing muscle means that ATPase histochemistry protocols can not be uncritically applied to developing muscles. The ATPase procedure can be adapted for use with embryonic muscles (McLennan, 1983a), but this has rarely been done. When the adult form of ATPase histochemistry is inappropriately used on myotubes, all myotubes appear to be fast fibres, even though they all contract slowly (review: McLennan, 1990b). These artifactual results gave rise to the erroneous belief that fibre types do not differentiate until very late in muscle development. When appropriate techniques are used, distinct but immature fibre types can be detected from the earliest stages of muscle formation (see below).

Muscle development

The immature fibre types are inexplicably intertwined with the subpopulations of myoblasts (mononucleated muscle precursors) and myotubes. Thus, before reviewing immature fibre types we will first outline the salient features of the myoblast and myotubal subpopulations. In this and subsequent sections, we will refer to studies of aves and small rodents. These studies have revealed some species differences, the significance of which is not understood. However, it is possibly important to point out that aves have two types of slow fibres: multiply-innervated, tonic fibres and twitch fibres, which are very similar to their mammalian counterparts (Barnard et al., 1982).

Myoblast subpopulations

There are three broad subtypes of myoblasts: (1) early (also called embryonic or primary), which are the only myoblasts present during primary myotube formation; (2) late (fetal or secondary), which are the most abundant myoblasts during secondary myotube formation; and (3) adult (satellite cells), which are present in adult muscles (reviews: McLennan, 1990a; 1994; Stockdale, 1992; Miller, 1992; Hauschka, 1994)

Early, late and adult myoblasts isolated from limb muscles can be distinguished based on their different culture requirements, abilities to fuse, sensitivities to growth factors, acetylcholine and phorbol esters, and the morphologies of the myotubes that they give rise to (McLennan, 1994). For example, avian early myoblasts usually require conditioned medium to fuse and form short myotubes with few nuclei whereas late and adult myoblasts fuse to form long, multinucleated myotubes, without the need for exposure to conditioned medium (Bonner and Hauschka, 1974).

Most importantly, in terms of this review, the various myoblast subtypes reproducibly develop into myotubes which express specific isoforms of myosin. When early myoblasts from chicken embryos are cloned, three types of myoblasts can be identified. One type of early myoblast exclusively gives rise to myotubes which only synthesise slow MHC. A second subtype gives rise to myotubes which only produce a "fast" MHC (probably embryonic MHC) whereas a minor third subtype gives rise to myotubes which synthesis both "fast" and slow MHC. In contrast, the myotubes formed from fetal myoblasts are all of a single type, which initially express only "fast" MHC but subsequently express slow MHC as they mature (Miller and Stockdale, 1986; review: Miller, 1992).

Mammals also have distinct early and late myoblasts but, unlike aves, there appears to be only one type of early myoblast. Mammalian early myoblasts form myotubes which synthesis embryonic and I/β MHC but not neonatal MHC whereas myotubes derived from late myoblasts synthesise neonatal MHC but not I/β MHC (Cho et al., 1993; Pin and Merrifield, 1993).

Heterogeneity of adult myoblast also exists with adult myoblasts of the cat jaw muscle and avian tonic muscles expressing the myosins that are peculiar to these muscles (Feldman and Stockdale, 1991; Hoh and Hughes, 1991). There may also be subpopulations of limb adult myoblasts with intrinsic commitment to a fast or slow lineage (Dusterhoft and Pette, 1993; Yao et al, 1994; Rosenblatt et al, 1996). However, Hughes and Blau (1992) have clearly shown that in vivo the progeny

of a single adult myoblast fuse into fibres with diverse fibre types, thus ruling out the possibility that slow and fast fibres grow by absorbing only adult myoblasts which are intrinsically matched to their fibre type.

Types of myotubes

Myotube formation in vivo is biphasic in small animals and probably multiphasic in human and other large animals. The first wave of (primary) myotubes form by the end-to-end fusion of myoblasts. After a period of development in which no new myotubes are produced, myoblasts accumulate on the surface of primary myotubes and fuse to form a new generation of (secondary) myotubes. In all muscles, there are many more secondary myotubes than primary myotubes (reviews: McLennan, 1990a, 1994). Primary and secondary myotubes differ in the characteristics of their originating myoblasts (see below), MHC expression (next paragraph) as well as various other properties, the most notable of which is their differential dependence on innervation (Harris, 1981; McLennan, 1983c; review: McLennan, 1994).

In rat muscles, all primary myotubes initially express both slow and embryonic MHC isoforms whereas the secondary myotubes initially express embryonic and neonatal MHCs. As myotubes mature, the MHCs expressed by them change. For instance, with slow primary myotubes there is a rapid and progressive loss of embryonic MHC which is nearly complete before birth whereas fast primary myotubes progressively replace their slow MHC with neonatal MHC, creating myotubes expressing trace levels of slow MHC and larger quantities of embryonic and neonatal MHCs (Narusawa et al., 1987; Harris et al., 1989; Condon et al., 1990). The embryonic and neonatal MHCs are subsequently replaced by IIa, IIb or IIx MHCs. During this process fibres can coexpress several isoforms: most commonly this will involve a fibre expressing various amounts of embryonic, neonatal and either IIa, IIb or IIx MHC but some fibres also transiently coexpress various amounts of IIa, IIb and IIx MHCs (LaFramboise et al., 1991; Zardini and Parry, 1994).

Diversity of myosin expression occurs at a very early stage of avian myogenesis. In chickens, primary myotubes in presumptive fast and slow muscles initially express a slow (S1), an embryonic-fast and a ventricular-like MHC (Bandman and Bennett, 1988; Sweeney et al., 1989; Page et al., 1992). Primary myotubes in presumptive slow muscles also express a second slow MHC (S3), which is similar or identical to atrial MHC (Crow and Stockdale, 1986a; Page et al., 1992; see also Kilby and Dhoot, 1988). The expression of S3 MHC begins prior to the cleavage of the premuscle masses into discrete muscles (Page et al., 1992), at which stage only 1-2% of myotubes have formed. S1 and S3 MHC are both developmental isoforms and are largely replaced in mature slow fibres by S2 MHC (Matsuda et al., 1982; Page et al., 1992).

S1 MHC is eliminated from avian fast fibres as they mature. The pattern of expression of the fast MHC isoforms is, however, more variable. In some fast muscles, the embryonic fast MHC is replaced with a neonatal isoform, which in turn is replaced by an adult fast isoform. In other fast muscles, fibres express either embryonic MHC, neonatal MHC or combinations of the various fast MHC isoforms (Crow and Stockdale, 1986b; Bandman and Bennett, 1988; Horn and Crow, 1989).

Relationships between developing and mature phenotypes

Primary myotubes originate by the fusion of early myoblasts and then subsequently absorb numerous late myoblasts and even larger numbers of adult myoblasts (Wigmore et al., 1992; Evans et al., 1994; Zhang and McLennan, 1995). Secondary myotubes are thought to originate exclusively from late myoblasts, although this has yet to be fully proven (see McLennan, 1994) and to grow by absorption of large numbers of adult myoblasts. Several important points can been drawn from these observations.

First, each muscle fibre is derived from more than one type of myoblast and the precursors to a single muscle fibre can be heterogeneous. To illustrate this point we will consider in detail the development of primary myotubes. Initially, the nuclei of primary myotubes are solely derived from early myoblasts: when early myoblasts fuse exclusively with other early myoblasts in vitro the resulting myotube synthesises both embryonic and I/β MHC, which is the phenotype of an immature primary myotube in vivo (see above). But as primary myotubes grow they absorb late myoblasts. When late myoblasts fuse exclusively with other late myoblasts in vitro the resulting myotube begins by synthesising only neonatal MHC. But what happens when a late myoblast fuses with an existing myotube containing nuclei derived from early myoblasts? The primary myotube will progressively move from having nuclei which were solely from early myoblasts to having a majority of nuclei from late myoblasts. By the time it is fully mature, >90% of its nuclei will be from adult myoblasts. Does the fusion of late and adult myoblasts into a primary myotube trigger changes in its characteristics?

The issues discussed in the previous paragraph raise a fundamental question about the biology of syncytia. That is, do the nuclei of syncytia function independently of each other - are parts of a muscle fibre under control of nuclei derived from early myoblasts ("early" nuclei), with other parts of a fibre being under control of nuclei derived from late or adult myoblast ("late" and "adult" nuclei, respectively)? Or do the nuclei in synctia co-operate by sharing the proteins which regulate gene expression? If the latter is occurring, is the mature characteristics of a muscle dominated by nuclei from its founding myoblasts or "adult" nuclei? "Adult" nuclei are numerically dominate in a mature fibre but the founding

nuclei could exert a profound influence - the nucleus from the first late myoblast to fuse with a primary myotube enters a cytoplasm containing proteins exclusively from "early" nuclei. If the cytoplasm contains nuclear binding proteins that reprogram "late" or "adult" nuclei into "early" nuclei then the fibre will be dominated by the characteristics of "early" nuclei, no matter how many late or adult myoblasts fuse with it. Probably, the mature characteristic of a fibre is multifaceted with some characteristics being determined by the originating nuclei, some by the properties of the numerically dominant nuclei (from adult myoblasts) and some being generated by the environmental influences on the fibre.

It is unresolved whether the characteristics of myotubes are solely determined by their originating myoblasts. In mammals, primary myotubes can develop into fast or slow muscle fibres. Consequently, it has been widely assumed that "slow" and "fast" early myoblasts exist. However, to date no published study has been able to detect more than one type of early myoblasts (review: McLennan, 1994), although this may merely reflect our incomplete knowledge of developmental isoforms of slow MHCs (Dhoot, 1994). A similar situation exists with respect to secondary myotubes and "slow" and "fast" late myoblasts. In contrast, the data from the study of aves is much clearer. Avian presumptive fast and slow primary myotubes express different myosins isoforms from an early stage of differentiation (Page et al., 1992) and distinct slow, fast and slow/fast early myoblasts exist in avian muscles (see above).

Irrespective of the species, it is likely that the local environment plays an important role in determining myotubal fibre type. The fibre type of a myotube is correlated with (1) its time of formation and (2) its position. Most primary myotubes develop into slow fibres. The exceptions to this rule is when primary myotubes develop in a region of a muscle which consists entirely of fast fibres. Similarly, secondary myotubes tend to develop into fast fibres, with secondary myotubes only developing into slow fibres in muscles, such as the soleus, which contain a high proportion of slow fibres. Slow secondary myotubes never develop adjacent to fast primary myotubes (McLennan, 1983b).

The nature of the environmental influence which determines whether a myotube is presumptive fast or slow has not been extensively studied. In particular, it is not known whether the environment influences myoblasts or myotubes: the distribution of fibre types could be an indirect result of "fast' and "slow" myoblasts being restricted to discrete areas of a muscle or, alternatively, local signals could directly control the characteristics of myotubes. One potential environmental influence is muscle use/neural activation. In the adult, the pattern of activation of a muscle fibre profoundly affects its fibre type (Buller and Eccles, 1960; Pette and Staron, 1997). However, the pattern of activation of developing muscles is quite distinct from the mature situation (Landmesser and O'Donovan, 1984) and denervation of a developing muscle does not alter the initial fibre type of a myotube (Butler et al., 1982).

Fate of myotubal fibre types

In the following discussion, we use the terms "intrinsic" and "extrinsic" fibre types. We define intrinsic fibre type as the original characteristics of a fibre whereas the extrinsic fibre types is the fibre type imposed on a fibre by outside influences, particularly its pattern of use.

It is likely that for most fibres the intrinsic and extrinsic fibre types are the same. For this to be occurring, myotubes with an intrinsic slow phenotype must be selectively innervated by "slow" motoneurones (McLennan, 1983b). The rat extensor digitorum longus (EDL) is a fast muscle with a small percentage of slow fibres in its deep portion. All of these slow fibres are derived from primary myotubes and express a slow phenotype from the earliest stages of development. That is, these fibres have an intrinsic slow phenotype. They must also be innervated by "slow" motoneurones as slow fibres transform when innervated by "fast" motoneurones.

Although most primary myotubes in the deep portion of the rat EDL retain their slow phenotype a small proportion of them slowly transform into fast fibres. In some muscles, transformation of fibre type is more extensive (Maltin et al., 1989). Here, the intrinsic fibre types are probably being over-ridden by extrinsic influences.

In conclusion, some fast fibres in mature muscles are of primary myotubal origin, some of secondary myotubal origin, some have an intrinsic fast phenotype and some have a intrinsic slow phenotype. Slow fibres are similarly diverse. One of the more vital questions to be answered is whether all of the fast (or slow) fibres are identical or whether they are subtly different depending on their developmental histories. Our preliminary investigations suggest that the latter is the case with the myotubal origin of a fibre being particularly important in situations when extrinsic influences are weakened (eg, such as after tenotomy) (Zhang, 1996).

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