It is generally agreed that successful skeletal muscle regeneration following intense exercise or injury is facilitated by the protein synthesis machinery and the recruitment of myogenic stem (satellite) cells. Upstream activation of these processes, however, is poorly understood. A growing body of evidence suggests cyclooxygenase (COX) activity plays an important role, as COX inhibition via nonsteroidal anti-inflammatory drugs (NSAIDs) has been shown to blunt load-mediated muscle protein synthesis rates (12). These drugs markedly inhibit COX-mediated synthesis of prostaglandins (11,13), which may be necessary to initiate the acute increases in muscle protein synthesis following high-intensity muscle contractions and/or injury. In addition, a role for prostaglandins in cardiac muscle hypertrophy via increased protein synthesis has been established (2,4,5). While the aforementioned human skeletal muscle studies (11-13) have focused on metabolic responses to acute mechanical overload, recent evidence in the rat model of chronic mechanical overload (synergist ablation) clearly demonstrates that chronic ibuprofen administration blunts the long-term skeletal muscle hypertrophy adaptation (9). This latter finding raises the question of whether COX inhibitors impair in vivo satellite cell recruitment in addition to their established inhibitory effects on muscle protein synthesis. Based on evidence in cultured rodent satellite cells (6), inhibition of satellite cell proliferation, differentiation, and/or fusion might be expected with NSAID treatment in humans in vivo; however, this has yet to be evaluated until recently.
The interesting work of Mackey et al. (3) is the first to demonstrate an impaired satellite cell response with NSAID treatment in humans following exercise. Trained endurance athletes showed a 27% increase in satellite cell number 8 days after a 36 km run, and this response was completely abolished by indomethacin treatment. While indomethacin is a non-selective COX inhibitor, there is evidence that COX-mediated prostaglandin synthesis during muscle regeneration may be preferentially driven by the COX-2 isoform (1). Treatment with a selective COX-2 inhibitor would therefore be a valuable follow-up to Mackey’s work.

Skeletal muscle satellite cells are traditionally thought to serve two major purposes in adult muscle: 1) Aiding in repair or regeneration following focal myofiber damage (1); and 2) Serving as nuclear donors during extensive myofiber growth that appears to be facilitated by myonuclear addition (8). Apart from the novel results regarding satellite cell inhibition by indomethacin, the work of Mackey et al. presents a number of noteworthy findings. First, satellite cell number increased in response to a single endurance exercise bout. As suggested by the authors, the endurance exercise bout appears to have activated some resident satellite cells from quiescence to re-enter the cell cycle leading to proliferation. A major question is why? This mode of exercise is not typically associated with myofiber hypertrophy—certainly not the degree of hypertrophy that is thought to require myonuclear addition to support growth. Further, activation this early (following a single exercise bout) would not likely be needed for myonuclear addition even if the stimulus were more appropriate for hypertrophy (e.g. resistance exercise) since most myofibers have room for expansion prior to reaching a theoretical myonuclear domain “ceiling” (7,8). Thus, the increased number of satellite cells in this model probably served an alternate purpose.

One logical explanation would be to support regeneration of damaged myofibers following the extensive run. However, this is not supported by the second major finding in this work. Irrespective of NSAID or placebo treatment during the days following the run, the number of regenerating myofibers was negligible and did not differ from baseline (as indicated by 0-0.52% of myofibers positive for embryonic myosin heavy chain and a small and unchanging percentage of myofibers with centrally-located nuclei).
This is not surprising since the subjects studied were trained endurance athletes, a novel feature of the paper. The young (25 yr), trained runners (VO2peak ~ 62 ml O2/kg/min) were studied while preparing for a 36 km race; thus a fair amount of protection against myofiber damage would be expected. Essentially, these athletes were accustomed to the exercise, which is not typical of most human studies of satellite cell activity. If not to support hypertrophy or damage repair/regeneration, why the (albeit modest) increase in satellite cell number? While this intriguing question cannot be answered by the histological data in Mackey et al., the paper certainly points to the possibility of a yet-to-be-defined function of resident skeletal muscle satellite cells.

The satellite cell findings highlighted are based strictly on the cells revealed immunohistochemically by a primary antibody against neural cell adhesion molecule (NCAM). This group and others have used NCAM immunoreactivity to identify a population of cells architecturally positioned beneath the basal lamina that are generally presumed to be skeletal muscle satellite cells. However, the ideal marker of satellite cells is a subject of continued debate. An additional strength of this work is the authors’ comparative study of NCAM+ cells vs. fetal antigen-1 (FA1)+ cells. While the majority of NCAM+ cells were also FA1+, a fair number of FA1+ cells were found outside of the merosin-labeled basement membrane. While the authors speculate that these FA+ (NCAM-) cells may represent a precursor cell subpopulation of myogenic lineage, it is entirely possible that non-myogenic cells were labeled by FA1 in addition to the “classic” skeletal muscle satellite cells.

The fact that the increased (NCAM+) satellite cell number was blunted with NSAID treatment, even in the absence of visible myofiber necrosis or detectable increases in regeneration, suggests COX-mediated prostaglandin synthesis may be initiated simply by exercise or, as the authors point out, indomethacin may have influenced the function of other pathways independent of COX/prostaglandin that caused the inhibition. These alternate pathways have received limited attention relative to studies of COX-dependent effects; however, their investigation in exercise models is warranted particularly since individual NSAIDs have varying influences on cell cycle regulators and transcription factors (10). Overall, the thought-provoking work of Mackey et al. should stimulate further in vitro and in vivo investigations to
enhance our understanding of these myogenic cells and the negative influence(s) of specific NSAIDs. Several questions remain regarding the underlying mechanisms of individual drugs, but these human data are an important addition to the mounting evidence that NSAIDs in general may extinguish the fire sparking skeletal muscle adaptations to exercise.

REFERENCES


