Dual effect of HGF on satellite/myogenic cell quiescence. Focus on “High concentrations of HGF inhibit skeletal muscle satellite cell proliferation in vitro by inducing expression of myostatin: a possible mechanism for reestablishing satellite cell quiescence in vivo”

Bénédicte Chazaud
INSERM U567, Centre National de la Recherche Scientifique UMR8104, Institut Cochin - Département Génétique et Développement, Université Paris Descartes, Paris, France

ADULT SKELETAL MUSCLE shows a very high level of plasticity that is necessary for adaptation to various conditions. Moreover, it possesses the remarkable capacity to regenerate after injury, and such plasticity derives from the properties of satellite cells—a group of cells that restore muscle function throughout their lifespan. Normally quiescent under steady-state conditions, satellite cells are activated following muscle damage or exercise and then begin to proliferate. Expansion of these myogenic progenitors promotes muscle repair and regeneration by committing them to myogenic differentiation while a subset do not differentiate but instead, replenish the satellite cell pool (8, 17). Although myogenic cell proliferation and differentiation have been extensively studied, the mechanisms that mediate the regulation of exit from and entry into quiescence are less characterized.

Previous studies have shown that low concentrations of hepatocyte growth factor (HGF) (a multifunctional cytokine originally named for its ability to promote the growth of hepatocytes) is one of the first cues, with release of nitric oxide involved in the activation (i.e., exit from quiescence) of satellite cells (12–14). In the present study published in American Journal of Physiology-Cell Physiology, Yamada et al. (15) show that concentrations of HGF above 20 ng/ml trigger a quiescence signal in primary myogenic cells from adult rats and that this occurs following the synthesis of myostatin (2, 16). Yamada et al. find that in myogenic cells stimulated with HGF, the expression of MyoD and myogenin, two master myogenic regulatory transcription factors (myogenic regulatory factors, MRFs), is dramatically decreased, in keeping with the self-renewing/quiescent status. Blocking antibodies against myostatin prevent the effects of HGF on myogenic cell quiescence and MRF expression. Moreover, the effects of HGF are reversible because myogenic cell proliferation can be reactivated following treatment with a low concentration of HGF.

These results highlight an exciting aspect of the regulation of precursor cell fate by the concentration-dependent, dual action of the same growth factor. To explain the opposite biological activities of HGF on myogenic cells, the authors propose the existence of two HGF receptors: 1) the well-known high-affinity c-met receptor that triggers activation of satellite cells observed at low HGF concentration and 2) another as-yet unknown, low-affinity receptor that induces myostatin expression and/or quiescence of signaling into myogenic cells at high HGF concentrations. Although the existence of this low-affinity receptor remains to be established, the current study raises new questions regarding the in vivo regulation of the local extracellular concentration of HGF. In normal muscle under steady-state conditions, HGF concentration is normally in the picogram per millimeter range, but upon damage, the HGF level can increase to nanogram per millimeter levels that are required to induce satellite cell activation (12). Yamada et al. show that HGF induces an autocrine amplification loop, thus provoking accumulation of HGF in the extracellular milieu (12). The source of HGF is not limited to myogenic cells: inflammatory cells, including monocytes/macrophages that are activated during muscle regeneration (3), also contribute to its generation (7, 9).

The study of Yamada et al. suggests that accumulation of HGF during muscle regeneration induces the quiescence of myogenic cells rather than further stimulating them. Nevertheless, kinetic analysis of in vivo events would be interesting to know: i.e., is a “high” range of HGF concomitant with the entry into quiescence of satellite cells at the end of muscle repair? Another question raised by the study is whether there is a subset of cells targeted by the high HGF effect. It is generally thought that after a proliferative phase, only a subset of cells enter into quiescence to replenish the satellite cell pool (1, 6, 18). In their study, Yamada et al. show that all the cells have reduced proliferation in response to high HGF and in addition, have decreased MyoD expression and increased myostatin concentration, implying that all the cells can self-renew. However, if one considers that HGF concentration progressively increases first in an autocrine fashion and subsequently with the presence of infiltrating myeloid cells, the temporal response of myogenic cells to high HGF concentration needs to be analyzed, and such studies should be undertaken at the times of terminal differentiation and self-renewal. Indeed, temporal control of myogenesis has been shown for regulatory molecules such as Notch and Wnt. Proliferation of myogenic cells depends on Notch signaling, while the subsequent differentiation phase is under the control of Wnt signaling (4). Appropriate timing of signaling of both Notch and Wnt is crucial for the correct sequence of events in myogenesis (4).

“Dual control” of myogenesis has been shown for some growth factors and is best described with TNF-α. At low concentrations, TNF-α stimulates myogenic differentiation through activation of p38 MAPK pathways. At higher concentrations, TNF-α is a potent mitogen for myogenic cells and inhibits myogenic differentiation (5, 10, 11, 19). As with HGF,
low concentrations of TNF-α may be generated in an autocrine fashion at the time of satellite cell activation. However, higher concentrations are likely to derive from inflammatory cells such as macrophages, which secrete TNF-α at the start of the muscle regeneration process (3).

Although further analysis is required to fully understand the kinetics and temporal regulation of HGF with respect to in vitro and in vivo myogenesis, the study of Yamada et al. is of importance. It is the first to show that the same effector is important. It is the first to show that the same effector is involved in both entry and exit into the quiescent state for satellite/myogenic cells, in a dual, and likely temporal fashion, depending on its concentration. Thus, when considering myogenic cells, in a dual, and likely temporal fashion, involving both entry and exit into the quiescent state for skeletal muscle injury switch into antiinflammatory macrophages to suppress inflammation (3).

REFERENCES


