certain: its role in cutaneous carcinogenesis is different from its role in cervical cancer.

Unlike cervical cancer, skin cancer related to HPV is probably caused by an interaction between the epidermodysplasia verruciformis types of HPV and ultraviolet radiation (see Figure). The early viral protein E6 of some types of HPV may impair the process of DNA repair or prevent apoptosis after exposure to ultraviolet radiation.[4,5] As a result, HPV-infected, DNA-damaged cells may survive and become genomically unstable. This instability may ultimately lead to actinic keratoses and squamous-cell carcinoma. Additional studies of the possible therapeutic and preventive effects of this α-lactalbumin–oleic acid complex on other HPV-related lesions seem to be warranted.

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1. Gibbs S, Harvey I, Sterling J, Stark R. Local treatments for cutaneous warts: systematic review. BMJ 2002;325:461.
2. Struijk L, Bouwes Bavinck JN, Wanningen P, et al. Presence of human papillomavirus DNA in plucked eyebrow hairs is associated with a history of cutaneous squamous cell carcinoma. J Invest Dermatol 2003;121:1531-5.
3. Feltkamp MC, Broer R, di Summa FM, et al. Seroreactivity to epidermodysplasia verruciformis-related human papillomavirus types is associated with nonmelanoma skin cancer. Cancer Res 2003;63:2695-700.
4. Iftner I, Elbel E, Schopp B, et al. Interference of papillomavirus E6 protein with single-strand break repair by interaction with XRCC1. EMBO J 2002;21:4741-8.
5. Jackson S, Harwood C, Thomas M, Banks L, Storey A. Role of Bak in UV-induced apoptosis in skin cancer and abrogation by HPV E6 proteins. Genes Dev 2000;14:3065-73.

Powerful Genes — Myostatin Regulation of Human Muscle Mass

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In this issue of the *Journal*, Schuelke et al. (pages 2682–2688) describe a child with substantial muscle hypertrophy and a splice-site mutation in the gene encoding myostatin. Myostatin is a member of the transforming growth factor β (TGF-β) family. Members of this family are diverse but have in common the regulation of growth and differentiation from the earliest stages of embryogenesis to mature adult tissues and cell types. Myostatin, or growth and differentiation factor 8 (GDF-8), was first defined as a negative regulator of muscle mass on the basis of a mouse model from which the gene encoding myostatin had been deleted. In these "mighty" mice, gross muscular hypertrophy develops; it has been attributed to an increase in the number of myocytes and an increase in the size of myofibers, or hypertrophy.[1]

The current report describes a child who was noted at birth to have unusual muscle definition and size. This child was found to have a homozygous g→a transition at nucleotide g.IVS1+5 in his myostatin gene. This base-pair alteration results in the missplicing of myostatin messenger RNA, thereby reducing the production of mature myostatin protein. At his current age of four years, the child continues to have enlarged muscle mass and is unusually strong. His mother is a heterozygous carrier of the same variant and is a former professional athlete. Other members of her family reportedly possess great strength. This genetic-association study, taken together with studies in animal models, argues strongly for a key role of myostatin-gene variants in the regulation of muscle size.

Many involved in agriculture already have an appreciation of myostatin-gene variants.[2] Several lines of "double muscling" cattle with naturally occurring myostatin-inactivating mutations have been described; notably, Belgian Blue cattle have long been valued for their profoundly enhanced muscle mass. The large size of Belgian Blue calves creates difficulty in maintaining this breed, since assistance may be required at delivery to minimize the risk of fetal and maternal loss. Multiple myostatin-gene variants generate muscle hypertrophy in animals, and most of these mutations reduce the production of mature myostatin. Intriguingly, while the loss of myostatin or myostatin inhibition leads to an increase in muscle mass, myostatin inhi-

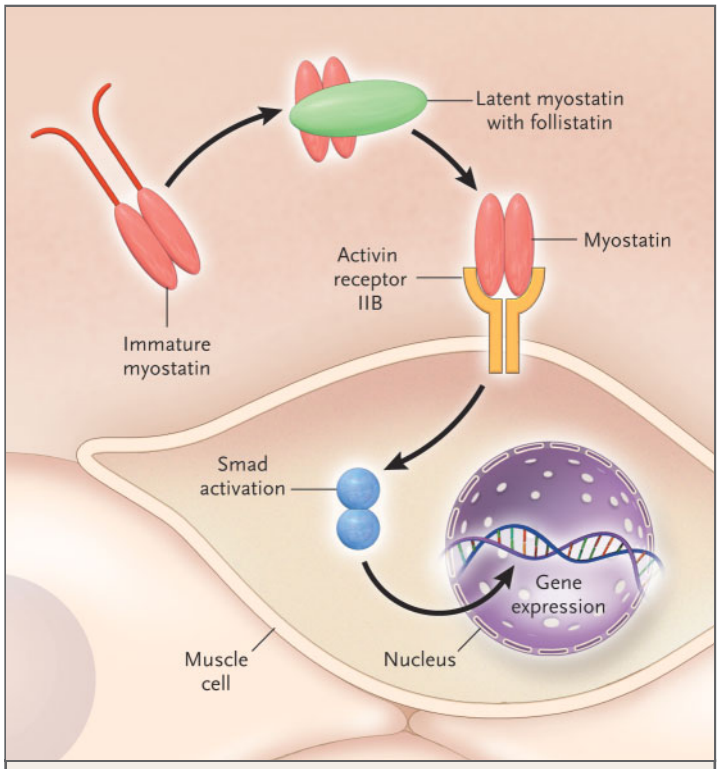

Figure. Myostatin Processing.

Mature myostatin is produced after dimerization and cleavage. Myostatin remains in a latent form in a complex with follistatin. Ligand binding to activin receptor IIB leads to Smad activation and changes in gene expression.

bition also results in a concomitant loss of adipose tissue.

Myostatin, like other members of the TGF-β family, is synthesized and secreted as an inactive propeptide. Myostatin dimerizes and is then cleaved to produce the mature form (see Figure). The latent form of myostatin binds to follistatin, which can inhibit myostatin function. Mature myostatin engages the myostatin receptor, activin receptor IIB. This receptor, like other TGF-β receptors, activates members of the Smad family to control gene transcription and mediate the effects of myostatin. The precise pathways by which myostatin is processed and the signaling cascade activated by receptor binding are equally important keys to the regulation of muscle mass.

Although mutations in the human myostatin gene may be relatively rare, more common variants may modestly reduce myostatin activity and result in a milder increase in muscle mass. Indeed, the mother of the child described by Schuelke et al. was heterozygous for the g.IVS1+5 g→a allele, yet she had enhanced athletic ability. The role of myostatin-gene polymorphisms in humans may be used to identify persons who are more likely to become successful athletes. Although the ethics of using such genetic information is questionable, the feasibility of identifying this information should not be doubted. The successful professional athlete is the product of both nature and nurture, requiring the correct genetic complement and the appropriate training milieu. However, second- and third-generation professional athletes are not unusual and may owe their prowess in part to natural selection for variants of genes such as the myostatin gene that confer a predisposition to enhanced athletic ability.

Myostatin inhibition is an important therapeutic target that may prove useful for the treatment of disorders that cause muscle degeneration. Even partial myostatin inhibition achieved through receptor-blocking antibodies can increase muscle mass in animal models of muscular dystrophy as well as in normal animals.[3] Myostatin blockade may be useful in the treatment of more common muscle-degenerative states, such as those that occur with aging.

Persons interested in performance enhancement are already aware of myostatin as a potential means of increasing muscle mass and strength. A number of products that are not approved by the Food and Drug Administration are widely available; their effectiveness and safety profiles have not been determined in humans or animals. Nonetheless, myostatin blockade will probably work its way into professional and amateur athletics, as well as into the ever-growing business of physical enhancement.

Whereas myostatin blockade is effective in increasing muscle mass, excessive myostatin leads to a decrease in muscle mass and function. The transgenic overexpression of myostatin results in cachexia in mice.[4] Thus, reduced muscle mass may be similarly associated with variants of the myostatin gene that cause elevated levels of myostatin protein and function. The identification of myostatin has highlighted a pathway that may yield many different regulators of muscle mass and may also influence adipocyte content. Other regulators of muscle mass, such as the insulin-like growth factor I pathway, have also received considerable attention because of their role in muscle biology. These two pathways, and others, may have additive or even

synergistic effects. Although these pathways hold great promise for the treatment of muscle-degenerative disorders, the potential for abuse outside of the medical arena is substantial, and further studies of the safety, efficacy, and long-term consequences of manipulating muscle growth are needed.

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1. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature 1997;387:83-90.

2. Dickman S. Gene mutation provides more meat on the hoof. Science 1997;277:1922-3.

3. Bogdanovich S, Krag TO, Barton ER, et al. Functional improvement of dystrophic muscle by myostatin blockade. Nature 2002;420:418-21.

4. Zimmers TA, Davies MV, Koniaris LG, et al. Induction of cachexia in mice by systemically administered myostatin. Science 2002;296:1486-8.