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"A rare disorder, yes; an unimportant one, never".

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Editorial

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The bizarre set of pathological manifestations—endocrine hyperfunction, skin hyperpigmentation, and fibrous dysplasia of bones—known as McCune-Albright syndrome (MAS[1]; reference 1), has been a source of fascination for over six decades. The investigations into its etiology reached a high point in 1975 when Happle (2) suggested that the distribution of pigmented areas along the dermatomes reflected the dorso-ventral outgrowth of two cell populations during development, and therefore represented cutaneous mosaicism. Happle also suggested that affected cells carry a dominant lethal gene mutation so that they only survive in the presence of unaffected cells. The studies reached another milestone in 1991 with the discovery of somatic mutations in the GNAS1 gene, encoding the α-subunit of the stimulatory G protein (3). The mutations, substitutions of either cysteine or histidine for arginine at position 201 in the Gsα-subunit, cause loss of GTPase activity and increased stimulation of adenylyl cyclase. The resulting overproduction of cAMP provides a straightforward explanation for the hyperactivity of affected endocrine organs and the increased proliferation of melanocytes and increased melanogenesis in affected skin areas.

While the R201C and R201H GNAS1 mutations in MAS have provided a unifying explanation for the endocrine and pigmentation abnormalities, they have not done the same for the crippling skeletal dysplasia that is part of the syndrome. This imbalance is now being corrected. In this issue of *The Journal*, an article by Bianco et al. (4) describes the use of a novel cell transplantation technique to examine the fibrous dysplasia in MAS. The results and their implications are exciting and provide an understanding of the cellular nature of the bone lesions in MAS for the first time. The paper also describes an experimental system that should facilitate dissection of the molecular pathogenesis of the skeletal anomalies and testing of novel therapies. In addition, the paper is likely to stimulate basic research of osteoblast differentiation and gap junction–mediated intercellular communication: it provides a model for studies of other skeletal syndromes that show a mosaic pattern of abnormalities, such as the Ollier, Maffuci, and Proteus syndromes, and it hints at the cellular and molecular mechanisms that regulate the formation of woven and lamellar bone during normal skeletal development.

What are the results? When Bianco et al. transplanted marrow stromal cells from normal donors (or cloned normal populations of cells isolated from the lesions of patients with MAS) into the subcutaneous tissue of immunocompromised mice, ossicles with a microstructure characteristic of lamellar bone were formed. These ossicles surrounded areas of adipocytes and hemopoietic cells, like normal trabecular bone with marrow. In contrast, with clonal populations of only mutant cells, the grafts failed and no human cells survived. When mixtures of wild-type and mutant (R201C or R201H) stromal cells were used, areas of bone having all the histological features of fibrous dysplasia were formed. Such lesions typically consist of areas in which normal bone and marrow are replaced by a cellular, fibrous tissue without hematopoiesis and adipogenesis (5). Mixtures of mutant and unaffected cells precisely replicated this abnormal structure in the transplants. Bone elements within the transplants consisted of woven bone with a covering of osteoblasts showing an abnormal, retracted appearance, and they were separated by a cellular, fibrous tissue.

What are the implications? First, the skeletal lesions in MAS are not clonal, but represent a mosaic of wild-type and mutant cells. Second, the presence of wild-type cells may indeed be required (as hypothesized by Happle [2]) for the survival of mutant cells, at least in the transplant environment. And third, the ossicles that form with a mixture of wild-type and mutant cells have abnormal structure, and the osteoblastic cells along their surfaces are abnormally retracted and spindle-shaped; therefore, a mixture of wild-type and mutant cells appears to be required for the abnormal ossicles to develop. The mutant cells (presumably the undifferentiated cells in the fibrous regions) may produce abnormal levels of cytokines that affect the shape and matrix production of wild-type osteoblasts (the cells that produce and cover the ossicles) or they may affect the wild-type cells more directly. An attractive possibility is that cAMP, at increased levels in mutant cells, is transported into wild-type cells through gap junctions between osteoblasts. It is known that increasing the level of cAMP in osteoblasts leads to decreased levels of cytoskeletal actin and myosin, causing cell retraction.

The inhibitory effect of the Gsα-mutations in MAS on differentiation of osteoblasts (6) raises obvious questions about the role of cAMP-dependent mechanisms in the differentiation of normal osteoblasts. The discovery that a transcription factor in the runt family, CBFA1, is required for osteoblast differentiation (7) makes CBFA1 a possible ultimate target for such cAMP-dependent signaling pathways. Negative regulation of CBFA1 through increased cAMP levels could occur at the level of transcription or at the level of protein stability. Recent studies (8) demonstrate that glucocorticoids cause a significant decrease in the protein levels of CBFA1 without affecting the levels of mRNA; cAMP could likewise affect the half-life of CBFA1 protein. Finally, since the ossicles formed with the mosaics of wild-type and mutant cells showed entirely woven characteristics, cAMP-dependent signals may be important in regulating formation of woven and lamellar bone during normal bone development and remodeling. It is well known that increased mechanical strain leads to the formation of woven bone (9). Therefore, it will be interesting to find out whether the response of bone to mechanical strain is regulated by cAMP-dependent mechanisms.

In 1975 DiGeorge (10) concluded an editorial by stating that MAS was "a rare disorder, yes; an unimportant one,

1. *Abbreviation used in this paper:* MAS, McCune-Albright syndrome.

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never." More than twenty years later, the statement still rings true and we look forward to future exciting installments.

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