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INSIDE LAB INVEST

NEW MOVES FOR AN OLD KERATIN: Keratin biology has proven to be a bountiful resource linking protein structure with pathogenesis. However, mysteries still remain. Investigation of keratin-15 (K15) has been hampered by the absence of mono-specific antisera. Earlier work led to a number of hypotheses about the functionality of this keratin. Partial co-localization with K14 had suggested a role in proliferation, and a cross-reactive antibody marked candidate hair follicle stem cells. In this issue of the journal, **Porter et al** use new K15-specific antibodies to determine the localization of K15 in human and rodent tissues (Lab Invest 2000, 80: 1701–1710). In human stratified squamous epithelium, K15 is restricted to the basal layer of the epidermis, even where K14 is present in suprabasal layers. Sweat glands showed discordant staining for K14 and K15 in myoepithelial cells and luminal cells, respectively. In wound healing, K15 is suppressed in migrating keratinocytes. Although K15 is expressed in basal cell carcinoma, there is no association of K15 with Ki67-positive cells in normal epidermis, so K15 is not linked specifically to proliferation. Finally, the widespread distribution of K15 indicates that it is unlikely to uniquely mark stem cells. The authors speculate that K15 expression occurs in a compartment of partially differentiated basal cells. Such cells might have rigid mechanical properties, maintained by K15, that stabilize the tissue architecture. This would hamper processes involving cell migration, including wound healing and cancer progression, so that these processes would require suppression or selection against expression of K15.

TELOMERE LENGTH AND VASCULAR DEMENTIA: Cell senescence and human senescence are not the same thing. The former refers to the observation that the replicative lifetime of certain mammalian (including human) cell types appears to be limited, after which cultured cells become morphologically and functionally abnormal. Cell senescence may have multiple causes, one of which is the progressive shortening of chromosomal telomeres during repeated rounds of replication. A common but not universal end point of human senescence is dementia. Dementia may arise from specific degenerative diseases of the brain (eg, Alzheimer's) or from numerous other causes, such as ischemia secondary to atherosclerosis of the brain vasculature (vascular dementia). In the current issue of the journal, **von Zglinicki and colleagues** (Lab Invest 2000, 80: 1739–1747) make a striking finding: the shortening of telomere lengths in peripheral blood mononuclear cells (PBMC) correlates with vascular dementia but not with dementia because of other causes or vascular disease in the brains of patients who do not show dementia. What is the explanation for this observation? The authors establish that there is a good correlation between telomere length in PBMC and skin fibroblasts from the same individuals, and therefore they infer that PBMC telomere length is also a useful surrogate for telomere length in brain cells. Telomeres generally shorten with age (which may reflect cell senescence), but not all individuals show this change at the same rate. More importantly, telomere shortening in fibroblasts reflects a loss of resistance to oxidative stress. This leads the authors to suggest that individuals with shorter telomeres in their PBMC are less resistant to ischemia and reperfusion in their brains, a cause of oxidative stress, and that such low-resistance individuals are more prone to develop dementia in the face of cerebrovascular disease. This is an intriguing hypothesis and provides yet another piece of indirect evidence for the potential value of antioxidant therapy as a treatment for human senescence. It still remains to be proven that such an approach has actual benefit.

B LYMPHOCYTE MODULATION OF BONE FORMATION—IMPLICATIONS IN HEALTH AND DISEASE: Interactions among immune and hematopoietic cellular elements and bone elements are well documented. Indeed, bone formation and resorption are mediated via cellular elements that are derived from hematopoietic precursors (in the case of osteoclasts) or are derived from marrow stromal elements (in the case of osteoblasts). In addition, many soluble factors that act as modulators of bone formation and resorption are produced by immune and hematopoietic cells. Over the past several years many studies have demonstrated that immunodeficiency states affect bone turnover. However, these studies have been controversial. For example, some studies have demonstrated decreased bone formation in athymic mice lacking T lymphocytes whereas

others have demonstrated normal bone turnover. Recent studies have suggested that B lymphocytes may also serve as regulators of bone resorption, and investigators have proposed links between estrogen's effects on B-cell lymphogenesis and bone resorption observed in estrogen deficiency. In light of these studies, **Marusic et al**, in this issue of the journal (Lab Invest 2000, 80: 1761–1774), hypothesized that B lymphocytes are involved in the regulation of bone formation by osteoblasts, presumably via factors produced by B lymphocytes that, in turn, would affect osteoblasts. Using B-cell–deficient mice produced by targeted disruption of the μ-chain (μMT mutation), which arrests B-cell development. These investigators assessed new bone formation in wild-type and μMT mice in two in vivo models: ectopic bone induction by bone morphogenic proteins and bone regeneration after bone marrow injury. Morphological assessments, as well as expression of bone specific proteins and inflammatory/immunomodulatory cytokines, were performed and demonstrated larger ossicle volume and mass, along with differences in inflammatory/immunomodulatory cytokines in μMT mice during development of the newly induced bone. These studies suggest that B lymphocytes may participate in the creation of the cytokine/growth factor milieu at sites of new bone induction. Furthermore, the presence, absence, or altered numbers and/or activation states of B-cell subsets may play significant roles in bone formation/resorption in health, as well as in a variety of disease states, including infectious, autoimmune, and neoplastic conditions. A better understanding of the dynamic, complicated, and complex interactions between the immune and skeletal systems may ultimately lead to novel and effective therapeutic approaches to the treatment and prevention of a variety of metabolic bone diseases.

A BIOLOGICAL MODEL FOR TUMOR PROGRESSION: One of the justifications for studying the two phases of the life of a tumor, promotion and progression, is the notion that understanding what makes cancerous cells acquire progressively more aggressive behavior will enable us to interfere with the forward forces or even reverse the process. In this issue of the journal, **Okada et al** report a laboratory model for studying the transformation of benign human tumor cells into cells with malignant phenotype (Lab Invest 2000, 80: 1617–1628). A cell line derived from a colonic adenoma can be transformed into adenocarcinoma if injected into nude mice in conjunction with a foreign body that elicits an inflammatory response. The work of **Okada et al** shows that it is the fibroblastic stromal response that is responsible for the effect and that activated murine fibroblasts secrete "factor(s)" that mediate the transformation. A preliminary characterization suggests that the factor is a protein with a size above 100 kDs and that its biological activity is neuroaminidase-resistant. Clearly detailed biochemical characterization of the molecule(s) responsible for the progression is needed, but with a relatively simple laboratory system at hand, further details should not be long in coming forth. Of interest is that the effect of the activated murine stroma induces genetically transmittable alterations in the adenoma cell line because the phenotypic malignant behavior remains unchanged after many passages of the cells in vitro. Dissecting the mechanistic details of the phenomenology reported by **Okada et al** should be eminently feasible and hopefully illuminating!