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SHUTTING DOWN HORMONE RESPONSES: Inactivation of tumor suppressor genes can be achieved by a variety of mutational mechanisms. However, it is now appreciated that restraint of such genes is often achieved through epigenetic, rather than genetic, means. A frequent mechanism is hypermethylation of CpG islands in the promoter, which interferes with transcription. Changes in the methylation state of CpG islands can be assayed using the sensitive and convenient method of methylation-sensitive polymerase chain reaction. Malignant progression of hormone-responsive tumors is often accompanied by loss of functional hormone receptors. In the case of prostate carcinoma, loss of androgen receptor (AR) contributes to the development of androgen-independence. Hypermethylation of CpG islands within the AR promoter was found in some AR-negative prostate carcinoma cell lines, suggesting that this may be a mechanism for loss of AR during progression to hormone-independence. In this issue, **Nakayama et al** (Lab Invest 2000, 80: 1789–1796) have now evaluated hypermethylation of CpG sites in primary and hormone-refractory prostate carcinoma tissue. Among ten primary tumors tested, one failed to express AR, and this was one of two primary tumors that were methylated in all three regions tested. Hypermethylation of the AR gene at one or more of the sites tested occurred at roughly the same frequency in hormone-refractory tumors. The DU145 prostate carcinoma cell line does not express AR mRNA. Treatment of these cells with 5′aza-2′deoxycytidine, which interferes with methylation, induced AR RNA expression. Histone deacetylation is another mechanism for silencing of genes in cancer, and it is noteworthy that Trichostatin A, which inhibits histone deacetylase, also partly reactivated AR expression. These results establish that hypermethylation of AR 5′ sequences does occur in a subset of primary and hormone-independent prostate carcinoma, but more work will be needed to determine whether this is a major determinant of androgen insensitivity. As the reactivation experiment demonstrates, epigenetic regulation is, by its nature, less permanent than mutation, so that reanimation of epigenetically suppressed genes may become an important therapeutic strategy.

DECORIN AND PERIODONTAL DISEASE: Periodontal diseases are common in the adult population, affecting approximately 10% of the population, increasing to more than 30% in individuals in the fifth decade or older. Although the etiology of periodontal diseases is considered to be infectious, there is evidence that susceptibility may depend upon genetic factors affecting tooth development. Indeed, patients with several inherited connective tissue disorders including osteogenesis imperfecta, infantile progeroid syndrome, and Ehlers-Danlos syndrome (EDS) types I and VIII experience abnormalities in tooth development and eruption. Further, patients with EDS types IV, VII, and IX have been reported to experience early onset of periodontitis. Thus, the concept that the composition/organization of connective tissue components plays significant roles in determining susceptibility/resistance to periodontal diseases is a reasonable one. In this issue, **Häkkinen et al** (Lab Invest 2000, 80: 1869–1880) use mice with targeted disruption of the decorin gene as a model to study the roles of this small leucine-rich proteoglycan, which is known to be present in periodontal tissue and to interact with several matrix molecules, in modulating the organization of collagen fibrils and fibroblast proliferation in the periodontal ligament. In their study, they found decorin-deficient animals to exhibit abnormal morphology and organization of the collagen fibrils and increased numbers of fibroblasts in the periodontal ligament. Because natural periodontal disease is rare in laboratory mice and an initial bacterial challenge appears to be a necessary prerequisite, the possibility exists that these and other genetically altered mice may be useful models of periodontal disease following a defined bacterial challenge. Such models should be of use in developing a more complete understanding of the roles of matrix composition/organization in these diseases as well as in the development and testing of treatment protocols aimed at blunting or ameliorating these diseases.

CAN ANTIGEN PRESENTING CELLS AID IN DIAGNOSIS? Organ-specific autoimmunity is often characterized by inflammatory infiltrates of mononuclear cells. In some cases, the infiltrate may be focal and hard to detect in a biopsy specimen. It is often easier to find such cells by staining the tissue with antibody to a T cell

marker such as CD3 (a pan T cell molecule) or CD45RO (a marker of T memory and effector cells), but the infiltrate still may be missed in a particular section. A crucial aspect of T cell responses to antigen, including autoantigen, is that T cells actually respond to fragments of macromolecules (usually peptides) that are processed and then displayed while bound to major histocompatibility complex (MHC) molecules expressed on the surface of another cell. Cells of the mononuclear phagocyte lineage, especially myeloid dendritic cells and inflammatory macrophages, are adept at presenting antigens to T cells and are therefore sometimes called professional antigen-presenting cells (APCs). This is because professional APCs not only efficiently process and display antigens but also provide essential antigen-independent signals (called co-stimulators) required for T cell activation. It follows that sites of T cell-mediated injury will not only contain infiltrating T cells but also will contain infiltrating APCs. In fact, in a number of model systems, eg, insulitis in mice and rats, APCs are the major infiltrating cell populations during the initial phases of the response when T cells are still difficult to detect. In the current issue of the journal, **van Blokland and colleagues** (Lab Invest 2000, 80: 1935–1941) test this idea in minor salivary glands involved with Sjögren's syndrome or with isolated focal lymphocytic sialoadenitis. They find that in these settings there are markedly increased numbers of both dendritic cells and inflammatory macrophages compared with control tissues, which are readily detectable by antibody staining. Furthermore, they find that detection of APCs is more sensitive than detection of T cells for making the diagnosis. This pilot study raises the possibility that APCs may be useful markers of organ-specific autoimmunity in other settings as well, eg, autoimmune thyroiditis. This surmise warrants investigation.

PARAFFIN BLOCKS TURN TO GOLD: One of the major concerns in biomedical translational research is the time that passes before advances in the understanding of disease are applicable to clinical practice. There are many factors responsible for the delay, but at present there is hope that new technologies, coupled with computational biology, will speed up the transition from discovery to application. These so-called high throughput technologies not only accelerate application but also facilitate discovery by enabling the quasi-simultaneous gathering of large data sets concerning a large number of study subjects. Until 1998, when a group of Finnish and Swiss investigators described tissue microarrays (TMAs), it was difficult to imagine how tissue analysis could be sped up. Once apprehended, it did not take long to realize that the clever invention of TMAs has many advantages. Cumbersome pathology archives can be literally rearranged by the construction of a single master array block that can easily house 800 or even 2,000 cases. These newly reordered tissue samples can be repeatedly re-examined, avoiding the time-consuming and error-prone process of filing and re-filing paraffin blocks. Extracting several "punch biopsies" from each original donor block creates several replicate master blocks that significantly extend the amount of tissue that can be made available to investigators, and yet, in most cases, it still preserves the diagnostic clinical value of the original specimen. In addition, the ability to go back to cases for which the outcome is known transforms inert case collections into precious tools for testing the predictive value of new biomarkers. In this issue, **Camp et al** (Lab Invest 2000, 80: 1943–1949) address some of the most troublesome issues linked to the use of TMAs as research tools: the preservation of antigenicity and the representativity of the tissue discs. At least for breast cancer, the data presented by **Camp et al** suggest that three cores per block are an adequate sample and that antigenicity is well preserved even after six decades of storage in paraffin. This is encouraging news for those wishing to unlock the potential for research held in the archives of most academic pathology departments.