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In this issue

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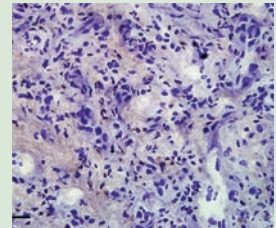




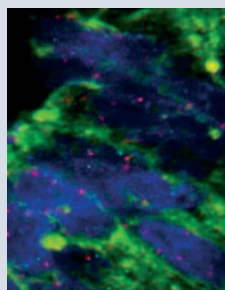
Cytokines swing between good and bad in the war on autoimmune arthritis

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A five-gene cancer-specific signature signs on in neoplasia



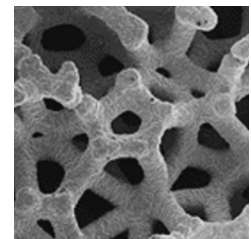
Unbiased screening for cancer-specific transcriptional signatures can help in patient management but can also assume homogeneity within populations; this can, in turn, decrease reliability of predictors when results are applied on a larger scale.

In this issue, Nicasio et al. undertook an approach based on a biased, rather than unbiased, screening of transformation-specific transcriptomes (pages 3015–3025). The researchers uncovered “shadow” oncogenic pathways contributing to the development of human malignancies and perhaps working in parallel with well-documented p53- and Rb-driven oncogenic pathways in human tumors. Using E1A, an early gene product of tumorigenic adenovirus, which transforms cells in culture and forces terminally differentiated cells to reenter the cell cycle, the authors identified a transcriptional signature in myotubes, then dissected the mechanisms responsible for activating the individual genes in the signature. Finally, they screened for alterations of the E1A-induced genes in naturally occurring cancers. This led to the identification of a cancer-specific signature composed of five genes induced by E1A that are overexpressed in a large fraction of cancers, correlating with tumor progression and unfavorable prognosis. One gene, called SKIN, was found to be a novel oncogene that represents the prototype of a bona fide cancer signature, causally involved in human cancer.

In vitro generation of human T cells not naive anymore

T cells are the front line of the human immune system, and their depletion can lead to life-threatening infections. Because the unique requirements for T cell development are so complicated, it has not been possible to generate these cells in vitro from bone marrow progenitor cells. The ability to do so would lead to significant advancements in the treatment of immune diseases. In this issue, Clark et al. report the development of an in vitro system for the production of diverse, functional, and self-tolerant human T cells from hematopoietic precursors (pages 3239–3249). Because the cells of human skin share many similarities with cells of the thymus — an organ required for T cell production — the authors used normal human skin keratinocytes and fibroblasts on a 3-dimensional matrix to support the complete process of T cell development from bone marrow-derived precursor cells.

This work provides evidence that skin and bone marrow biopsies can provide the starting material for generation of a new, patient-specific T cell repertoire. The use of naive, newly generated T cells could have broad clinical applications for a variety of diseases, including malignancies, autoimmune diseases, immunodeficiencies, and even transplant rejection.



Got milk? How breastfeeding affects HIV transmission

Mother-to-child transmission of HIV accounts for a large proportion of HIV infections in children, with many infected as a result of breastfeeding, which requires transfer of the virus across mucosal barriers. DC-SIGN, a DC lectin receptor, interacts with HIV and is found at high expression levels in tonsillar tissue. Now, Naarding et al. clarify how human milk affects the HIV interactions with DC-SIGN that occur during breastfeeding (pages 3256–3264). The authors show that human milk can block the binding of HIV to the DC-SIGN molecule expressed on dendritic cells and potentially inhibit the transfer of HIV-1 to CD4⁺ T lymphocytes. The authors identify the component present in human milk that binds to DC-SIGN. The inhibitory effect can be fully alleviated with an antibody recognizing the Lewis X sugar epitope on this factor. Other major milk proteins do not bind to DC-SIGN, nor do they inhibit viral transfer. These results demonstrate that protein-associated Lewis X is necessary and sufficient to interact with DC-SIGN and block the interaction of DC-SIGN and HIV. The identification of a factor in human milk that can block HIV-1 transmission, the ability of the factor to inhibit the virus from binding to DCs, and the potential immunomodulatory implications of such a compound have major implications for the development of agents that can block HIV transmission.