• Good review article of current theories on cancer and immunity.
• Underscores the importance of the functional competence of the cells involved, all of which are impacted by either immune aging and/or severe depletion.


Natural innate and adaptive immunity to cancer.
Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ.
Department of Pathology and Immunology, Washington University School of Medicine, Missouri, USA.

Abstract - The immune system can identify and destroy nascent tumor cells in a process termed cancer immunosurveillance, which functions as an important defense against cancer. Recently, data obtained from numerous investigations in mouse models of cancer and in humans with cancer offer compelling evidence that particular innate and adaptive immune cell types, effector molecules, and pathways can sometimes collectively function as extrinsic tumor-suppressor mechanisms. However, the immune system can also promote tumor progression. Together, the dual host-protective and tumor-promoting actions of immunity are referred to as cancer immunoediting. In this review, we discuss the current experimental and human clinical data supporting a cancer immunoediting process that provide the fundamental basis for further study of immunity to cancer and for the rational design of immunotherapies against cancer.

• Discusses importance and complexity of roles that CD4 T cells play in anti-tumor response. CD4 cells are one of the lymphocyte subsets known to be significantly affected (functional competence, as well as diversity) by both aging and immunodepletion.
• This review also highlights the vast array of subtypes of CD4 and CD8 T cells. Very little is known about the relative distribution of these within the body or the potential effects on particular subtypes as a consequence of repeated depletion of these cells from the circulation.

Immunol Rev. 2008 Apr;222:129-44.

Multiple roles for CD4+ T cells in anti-tumor immune responses.
Kennedy R, Celis E.
Mayo Vaccine Research Group, Mayo Clinic College of Medicine, Rochester, MN, USA.
Abstract - Our understanding of the importance of CD4+ T cells in orchestrating immune responses has grown dramatically over the past decade. This lymphocyte family consists of diverse subsets ranging from interferon-gamma (IFN-gamma)-producing T-helper 1 (Th1) cells to transforming growth factor-beta (TGF-beta)-secreting T-regulatory cells, which have opposite roles in modulating immune responses to pathogens, tumor cells, and self-antigens. This review briefly addresses the various T-cell subsets within the CD4+ T-cell family and discusses recent research efforts aimed at elucidating the nature of the 'T-cell help' that has been shown to be essential for optimal immune function. Particular attention is paid to the role of Th cells in tumor immunotherapy. We review some of our own work in the field describing how CD4+ Th cells can enhance anti-tumor cytotoxic T-lymphocyte (CTL) responses by enhancing clonal expansion at the tumor site, preventing activation-induced cell death and functioning as antigen-presenting cells for CTLs to preferentially generate immune memory cells. These unconventional roles for Th lymphocytes, which require direct cell-to-cell communication with CTLs, are clear examples of how versatile these immunoregulatory cells are.

• If a key way that tumors escape the immune system in the first place is by antigenic drift, this underscores the paramount importance of naïve T cells in the ongoing battle against this ever-changing tumor. As can be seen in the papers on immune aging and the consequences of lymphodepletion, naïve T cell functional capacity, as well as diversity of naïve T cell repertoire is significantly impacted by both of these.


**Antigenic drift as a mechanism for tumor evasion of destruction by cytolytic T lymphocytes.**

Xue-Feng Bai, Jinqing Liu, Ou Li, Pan Zheng, and Yang Liu

Division of Cancer Immunology, Department of Pathology and Comprehensive Cancer Center, Ohio State University Medical Center, Columbus, Ohio, USA

**Abstract** - It is established that mutations in viral antigenic epitopes, or antigenic drifts, allow viruses to escape recognition by both Ab's and T lymphocytes. It is unclear, however, whether tumor cells can escape immune recognition via antigenic drift. Here we show that adoptive therapy with both monoclonal and polyclonal transgenic CTLs, specific for a natural tumor antigen, P1A, selects for multiple mutations in the P1A antigenic epitope. These mutations severely diminish T cell recognition of the tumor antigen by a variety of mechanisms, including modulation of MHC:peptide interaction and TCR binding to MHC:peptide complex. These results provide the first evidence for tumor evasion of T cell recognition by antigenic drift, and thus have important implications for the strategy of tumor immunotherapy.

• Evidence for a crucial contribution of NK cells to tumor immunosurveillance. NK cells are also known to be affected by aging, though less is known about specific consequences of immunodepletion on this specialized subset of lymphocytes.


NK cells and cancer immunosurveillance.

Waldhauer I, Steinle A.
Department of Immunology, Eberhard Karls University of Tübingen, Tübingen, Germany.

Abstract
Natural killer (NK) cells are lymphocytes of the innate immune system that monitor cell surfaces of autologous cells for an aberrant expression of MHC class I molecules and cell stress markers. Since their first description more than 30 years ago, NK cells have been implicated in the immune defence against tumours. Here, we review the broadly accumulating evidence for a crucial contribution of NK cells to the immunosurveillance of tumours and the molecular mechanisms that allow NK cells to distinguish malignant from healthy cells. Particular emphasis is placed on the activating NK receptor NKG2D, which recognizes a variety of MHC class I-related molecules believed to act as 'immuno-alerters' on malignant cells, and on tumour-mediated counterstrategies promoting escape from NKG2D-mediated recognition.

http://www.nature.com/onc/journal/v27/n45/full/onc2008267a.html
• Pioneer experiment which proved, in genetically engineered mice, the involvement of the immune system in fighting cancer


**IFN\textgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity.**

Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD.

Abstract - Lymphocytes were originally thought to form the basis of a 'cancer immunosurveillance' process that protects immunocompetent hosts against primary tumour development, but this idea was largely abandoned when no differences in primary tumour development were found between athymic nude mice and syngeneic wild-type mice. However, subsequent observations that nude mice do not completely lack functional T cells and that two components of the immune system—IFN\textgamma and perforin—help to prevent tumour formation in mice have led to renewed interest in a tumour-suppressor role for the immune response. Here we show that lymphocytes and IFN\textgamma collaborate to protect against development of carcinogen-induced sarcomas and spontaneous epithelial carcinomas and also to select for tumour cells with reduced immunogenicity. The immune response thus functions as an effective extrinsic tumour-suppressor system. However, this process also leads to the immunoselection of tumour cells that are more capable of surviving in an immunocompetent host, which explains the apparent paradox of tumour formation in immunologically intact individuals.

http://www.nature.com/nature/journal/v410/n6832/full/4101107a0.html
The Immune System and Cancer: Consequences of Aging

These are a few papers specific to the topic, but it is discussed in many of the more general papers on immune aging and immune aging mechanisms.
The role of immunity in elderly cancer.
Malaguarnera L, Cristaldi E, Malaguarnera M.

Source
Department of Biomedical Sciences, University of Catania, Italy.

Abstract
The increased incidence of malignancies in elderly patients living in industrialized countries has led to both identify the causes that alter the normal homeostatic balance in elderly and designate the specific treatments. The progressive decline of the immune system (immunosenescence) involving cellular and molecular alterations impact both innate and adaptive immunity. The immunosenescence leads to increased incidence of infectious diseases morbidity and mortality as well as heightened rates of other immune disorders such as autoimmunity, cancer, and inflammatory conditions. Here, we summarize the knowledge on the major changes in the immune system associated with aging in primary lymphoid organs as well as a description of molecular mechanisms, and the impact on cancer development.

http://www.croh-online.com/article/S1040-8428(09)00122-X/abstract
Potential role of immunosenescence in cancer development.

Fulop T, Kotb R, Fortin CF, Pawelec G, de Angelis F, Larbi A.

Source
Research Center on Aging, Department of Medicine, University of Sherbrooke, Sherbrooke, Canada. tamas.fulop@usherbrooke.ca

Abstract
The incidence and prevalence of most cancers increase with age. The reasons for this may include tumor escape mechanisms and decreased immunosurveillance, but most are caused by the time required for carcinogenesis, according to most scientists. The immune system is a unique mechanism of defense against pathogens and possibly cancers; however, there is a body of evidence that the immune system of the aged is eroded, a phenomenon termed immunosenescence. There is a growing interest in immunosenescence and how it may contribute to the increased number of cancers with aging. Each arm of the immune system, innate and adaptive, is altered with aging, contributing to increased tumorigenesis. Understanding the contribution of immunosenescence to cancer development and progression may lead to better interventions for the elderly.

Immunosenescence: deficits in adaptive immunity in the elderly.

Hakim FT, Gress RE.

Source
Experimental Transplantation and Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. hakimf@mail.nih.gov

Abstract
Aging is associated clinically with increases in the frequency and severity of infectious diseases and an increased incidence of cancer, chronic inflammatory disorders and autoimmunity. These age-associated immune dysfunctions are the consequence of declines in both the generation of new naïve T and B lymphocytes and the functional competence of memory populations. These alterations collectively are termed immunosenescence.

Aging, immunity and cancer.

Hakim FT, Flomerfelt FA, Boyiadzis M, Gress RE.

Source
Experimental Transplantation and Immunology Branch, National Cancer Institute, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892-1907, USA.

Abstract
Immunosenescence, the progressive decline in immune function that develops with age, results from cumulative alterations in critical B- and T-cell subpopulations. Decreases in circulating memory B cells and in germinal center formation are evident in the elderly, possibly due to diminished follicular dendritic-cell function. T-cell dysfunction is associated with reduced thymic generation of naïve T cells, virus-induced expansion of terminal effectors and increased levels of memory cells producing type I and II cytokines. The diversity of the T-cell receptor repertoire is diminished by the first two changes, and elevated type I cytokines might contribute to the pro-inflammatory cytokine milieu present in the elderly.

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