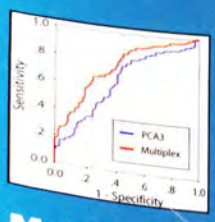
Number 3
Pages 627–956

Cancer Research



A Multiplex Urine Biomarker Analysis for Early Detection of Prostate Cancer
Page 645

Stromal Fibroblasts Promote Pancreatic Tumor Progression
Page 918

16-Kinase Gene Expression Identifies Luminal Breast Cancers with Poor Prognosis
Page 767

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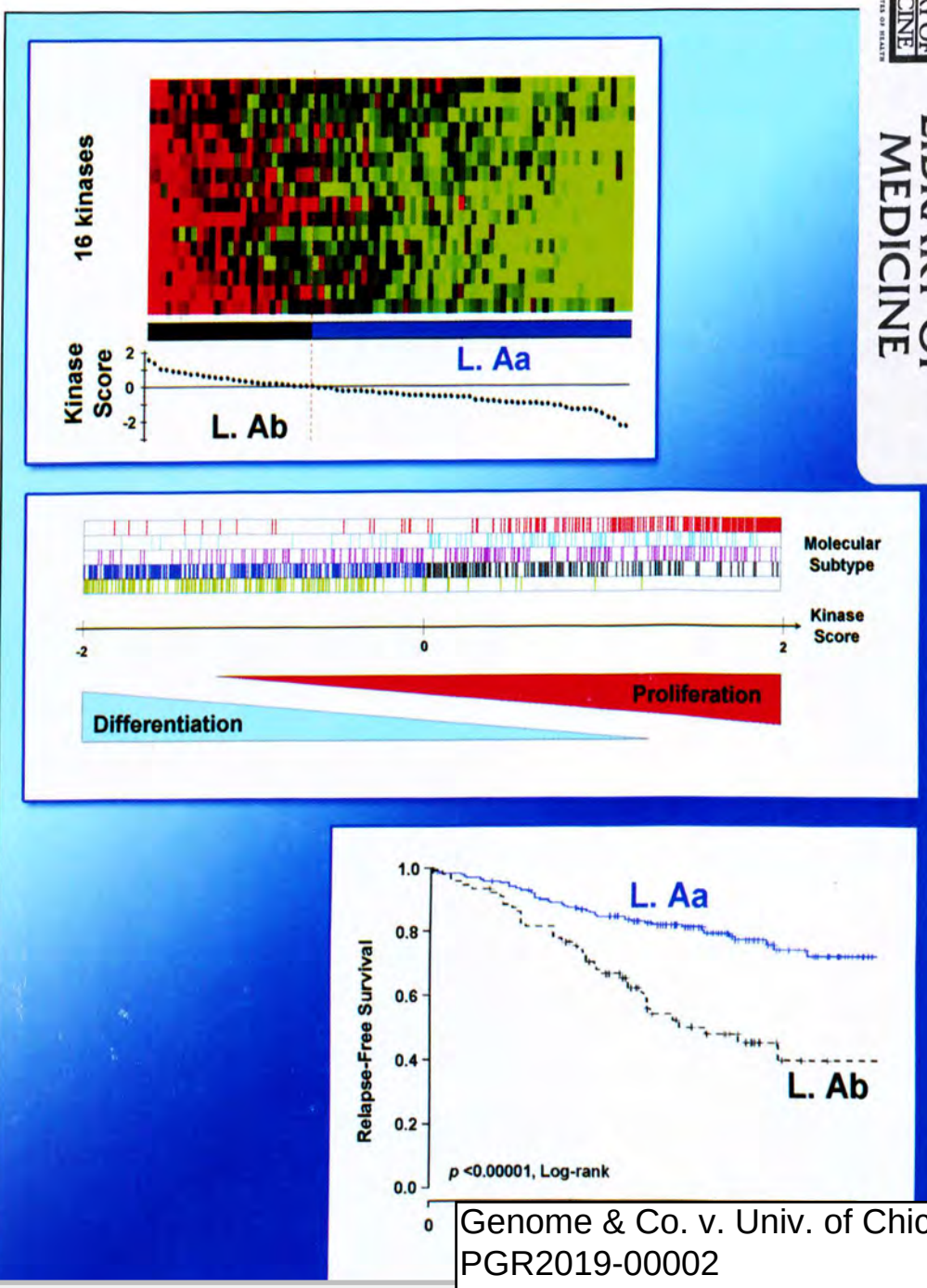

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Volume 68 · Number 3 **February 1, 2008 · Pages 627–956**

Reviews

Meeting Report

Priority Reports

Molecular Biology, Pathobiology, and Genetics

Cell, Tumor, and Stem Cell Biology

Contents (*Continued*)

Experimental Therapeutics, Molecular Targets, and Chemical Biology

Immunology

Endocrinology

Clinical Research

Epidemiology

Prevention

Corrections

Epitope Landscape in Breast and Colorectal Cancer

Neil H. Segal,[1,2] D. Williams Parsons,[1] Karl S. Peggs,[2,3] Victor Velculescu,[1] Ken W. Kinzler,[1] Bert Vogelstein,[1] and James P. Allison[2,3]

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Abstract

The finding that individual cancers contain many mutant genes not present in normal tissues has prompted considerable interest in the cancer epitope landscape. To further understand such effects, we applied *in silico*–based epitope prediction algorithms and high throughput post hoc analysis to identify candidate tumor antigens. Analysis of 1,152 peptides containing missense mutations previously identified in breast and colorectal cancer revealed that individual cancers accumulate on average ~10 and ~7 novel and unique HLA-A*0201 epitopes, respectively, including genes implicated in the neoplastic process. These data suggest that, with appropriate manipulation of the immune system, tumor cell destruction *in situ* may provide a polyvalent tumor vaccine without a requirement for knowledge of the targeted antigens. [Cancer Res 2008;68(3):889–92]

Introduction

Several classes of tumor antigens have been described and named according to their distribution in normal and neoplastic tissues. These include the shared differentiation antigens, such as melan-A/MART1 (1, 2) in melanoma; cancer testes or germ cell antigens, such as MAGE-1 (3) and NY-ESO-1 (4) in adult testes and diverse tumor types; and unique tumor antigens, which generally carry mutations, such as CDK4 in melanoma (5) and CASP-8 in head and neck cancer (6).

The immunogenicity of the unique tumor antigens was recognized in several seminal studies including animal transplant models (7) and chemically or UV light–induced tumors (8, 9). They are of particular interest because they result from somatic mutations in individual tumors and are absent from normal tissues (10, 11), providing antitumor specificity without anticipated deleterious autoimmunity. Somatic mutations can be classified as either "drivers" or "passengers". Passenger mutations provide no positive or negative selective advantage to the tumor but are retained by chance during cell division and clonal expansion. In contrast, driver mutations provide a selective advantage that promotes the tumorigenic process. The generation of mutations is continuous due to the imperfect nature of DNA replication and repair. Thus, the generation of additional antigens during tumor progression, whether driver or passenger (12), provides a continuously renewable source of antigen.

Recent analyses of breast and colorectal cancers showed a remarkable number of somatic mutations in human cancer (13). Among >13,000 genes analyzed, a total of 1,307 somatic mutations were identified in 11 breast and 11 colorectal cancers. Approximately 83% were missense mutations, 6% nonsense, and the remainder were insertions, deletions, duplications, and changes in noncoding regions. When extrapolated to the whole genome, it was calculated that individual tumors harbored an average of ~90 amino acid–altering (i.e., nonsynonymous) mutations. The kind of information available from such large-scale sequencing studies of individual tumors has not heretofore been available but clearly has implications for tumor immunity.

In the current study, we designed an *in silico* approach to examine whether the mutations identified in Sjoblom et al. (13) have the potential to generate novel epitopes that might serve as targets for an immune response. Using epitope prediction algorithms and high throughput post hoc analysis, we found evidence to support the notion that the human tumorigenic process results in the generation of multiple immune targets. Individual breast and colorectal cancers accumulated an average of ~10 and ~7 novel and unique HLA-A*0201 epitopes, respectively; several within genes that may be drivers. These results provide insights into the unique immune profiles of individual tumors with potential clinical relevance.

Materials and Methods

Epitope prediction. Peptide sequences corresponded to missense mutations identified during the discovery phase by Sjoblom et al. (13), flanked by up to 10 amino acids on either side. Concatamers of these peptides were analyzed with several epitope prediction algorithms for HLA-A*0201 binders. Major histocompatibility complex (MHC)-I antigenic peptide processing prediction (MAPPP; ref 14), developed at the Max-Plank Institute, facilitates the prediction of epitopes that can bind to MHC class I molecules based on a score calculated for each subsequence. Each amino acid at a specific position within a subsequence is given a value that has been precalculated and stored in static matrices. The precalculation was done either by BIMAS (15) or SYFPEITHI (16). Depending on the algorithm selected, the values were then multiplied (BIMAS) or added (SYFPEITHI) to determine the score for the subsequence. Peptides qualified as positive if they scored ≥100 and ≥24, respectively (17, 18). RANKPEP (19) uses specific scoring matrices from sets of peptides known to bind to MHC molecules as the predictor of MHC-peptide binding. Peptides qualified as positive if the percentage optimum was ≥50% or higher. NetMHC (20, 21) predicts peptide-MHC binding using artificial neural networks (ANN) and weight matrices. For ANN, used for HLA-A*0201 prediction, peptides scored positive if IC_{50} is ≤500.

Post hoc analysis. First, we searched for unique epitopes within concatamers of wild-type and mutant peptides. Epitopes identified in the "wild-type concatamer" included both true wild-type epitopes and artifacts across the concatenation sites and were removed from further analysis. The "mutant concatamer" was then used to search for remaining epitopes. To ensure that potential mutant epitopes did not span concatenation sites, the "mutant concatamer" used in this confirmatory phase included additional redundant characters spaced between peptides, thereby permitting confirmation of epitopes contained entirely within a mutant

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