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Senescence-associated-gene signature identifies genes linked to age, prognosis, and progression of human gliomas

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ABSTRACT

Background: Senescence-associated genes (SAGs) are responsible for the senescence-associated secretory phenotype, linked in turn to cellular aging, the aging brain, and the pathogenesis of cancer.

Objective: We hypothesized that senescence-associated genes are overexpressed in older patients, in higher grades of glioma, and portend a poor prognosis.

Methods: Forty-seven gliomas were arrayed on a custom version of the Affymetrix HG-U133 + 2.0 GeneChip, for expression of fourteen senescence-associated genes: *CCL2*, *CCL7*, *CDKN1A*, *COPG*, *CSF2RB*, *CXCL1*, *ICAM-1*, *IGFBP-3*, *IL-6*, *IL-8*, *SAA4*, *TNFRSF-11B*, *TNFSF-11* and *TP53*. A combined "senescence score" was generated using principal component analysis to measure the combined effect of the senescence-associated gene signature.

Results: An elevated senescence score correlated with older age ($r = 0.37$; $P = .01$) as well as a higher degree of malignancy, as determined by WHO, histological grade ($r = 0.49$; $P < .001$). There was a mild association with poor prognosis ($P = .06$). Gliosarcomas showed the

Abbreviations: CCL2, Chemokine (C–C motif) ligand 2; CCL7, Chemokine (C–C motif) ligand 7; CDK1NA, cyclin dependent kinase 1 nuclear antigen; CCL2, Chemokine (C–C motif) ligand 2; CCL7, Chemokine (C–C motif) ligand 7; CDKN1A, cyclin dependent kinase 1 A; COPG, coatomer protein complex, subunit gamma; CSF2RB, colony stimulating factor 2 receptor, beta; CXCL1, Chemokine (C–X–C motif) ligand 1; FDR, False discovery rate; ICAM-1, Inter-Cellular Adhesion Molecule 1; IGF, insulin-like growth factor; IGFBP-3, insulin-like growth factor binding protein-3; IL-6, interleukin-6; IL-8, interleukin-8; PCA, Principal component analysis; SAA4, Serum amyloid A protein-4; SAG, senescence associated gene; SASP, senescence-associated secretory phenotype; TCC, Total Cancer Care; TCGA, The Cancer Genome Atlas; TNFRSF-11B, tumor necrosis factor receptor super family 11B; TNFSF-11, tumor necrosis factor super family 11; TP53, tumor protein 53; WHO, World Health Organization.

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Interleukin-6
Senescence

highest scores. Six genes independently correlated with either age (*IL-6*, *TNFRSF-11B*, *IGFBP-3*, *SAA4*, and *COPG*), prognosis (*IL-6*, *SAA4*), or the grade of the glioma (*IL-6*, *IL-8*, *ICAM-1*, *IGFBP-3*, and *COPG*).

Conclusion: We report: 1) a novel molecular signature in human gliomas, based on cellular senescence, translating the concept of SAG to human cancer; 2) the senescence signature is composed of genes central to the pathogenesis of gliomas, defining a novel, aggressive subtype of glioma; and 3) these genes provide prognostic biomarkers, as well as targets, for drug discovery and immunotherapy.

1. Introduction

Older age is the most significant adverse prognostic factor for patients with gliomas .[1,2] More than any specific therapy, the histologic grade of the tumor and the patient's age are key prognostic factors that influence clinical outcomes.[3] Within each histologic type, the probability of survival is the lowest for those in older age-groups.[2] The average age for presentation of low-grade, diffuse astrocytomas (WHO II) is between 34 and 39, for anaplastic astrocytomas (WHO III) 40–46, and for glioblastoma (WHO IV), 61–62.[1,4,5] Classically, the median survival has been 5 years for WHO II, 3 years for WHO III, and one year for WHO IV.[3] The biological basis for the profound influence of the patient's age on glioma pathogenesis and prognosis is poorly understood.

In the current era of genomics and personalized medicine, we hypothesized that a specific class of genes, linked to cellular senescence, termed "senescence associated genes" (SAGs) plays a pivotal role in glioma biology, and the poor prognosis associated with advancing age. Senescence-associated genes, and the secretion of inflammatory cytokines linked to those genes, contribute to oncogenesis and malignant progression of several human cancers.[6–15] Senescent cells, paradoxically, can create a tissue microenvironment that promotes multiple stages of tumor evolution.[7–10,16–20] The senescence associated secretory phenotype (SASP), includes inflammatory cytokines, growth factors, and metalloproteases that also mediate several of the hallmarks of cancer[21,22]: angiogenesis, invasion, inflammation, and proliferation.

In this study, we hypothesized that senescence-associated genes are: i) overexpressed in older patients; ii) portend a poor prognosis and iii) are overexpressed in higher grades of glioma. To examine these possibilities, we made use of a repository of gene profiling data at the Moffitt Cancer Center.[22–25] We mined this database for a variety of human cancers, including gliomas, to determine a link, if any, between the senescence-associated gene expression, age of the patient, prognosis, and histological grade of the glioma.

2. Methods

The Total Cancer Care™ (TCC) research protocol of the Moffitt Cancer Center (http://www.moffitt.org/totalcancercare) functions as a comprehensive, prospective program to acquire tissues from patients undergoing cancer surgery at the cancer center or a TCC-collaborating site, linking molecular profiling, histopathological, and clinical data.[23] All participating patients provided written informed consent. The Institutional Review Board approved the protocol. In an initial phase of the study, we mined this resource to examine the gene expression profiles for 10 cancer types. In addition to the human gliomas, 4415 tumors were interrogated: lung (n ≅ 1100 cases); breast (n ≅ 1200); colon (n ≅ 700); kidney (n ≅ 600); prostate (n ≅ 220); ovary (n ≅ 230); pancreas (n ≅ 170); bladder (n ≅ 170); and liver (n ≅ 25).

We interrogated this unique resource to determine the gene expression profiles in patients with gliomas, centered on 14-genes associated with cellular senescence. We calculated a "senescence score", and correlated the senescence score with the patient's age, overall survival, and histological grade of the glioma. The mRNA microarray analysis was performed on 47 consecutive, histologically verified gliomas. The samples were arrayed on Rosetta/Merck Human RSTA Custom Affymetrix 2.0 microarray. The data was processed using robust multi-array average (RMA) algorithm.[26]

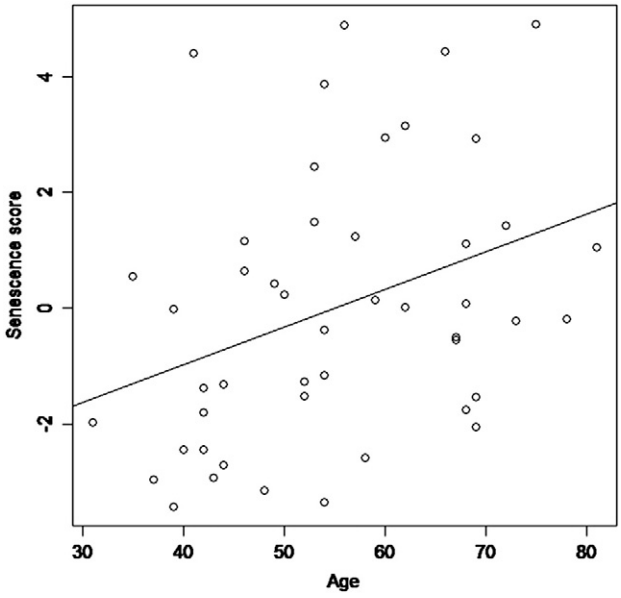

Fig. 1 – Senescence score using the composite value of the 14 senescence-associated-genes by the first principal component, correlated to patient's age. Spearman Coefficient = .37, *P* = .01.