THE MOFFITT CANCER CENTER TOTAL CANCER CARE RESOURCE: DISCOVERY OF A SENESCENCE-RELATED GENES SIGNATURE IN GLIOMAS.

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ABSTRACT

Background.

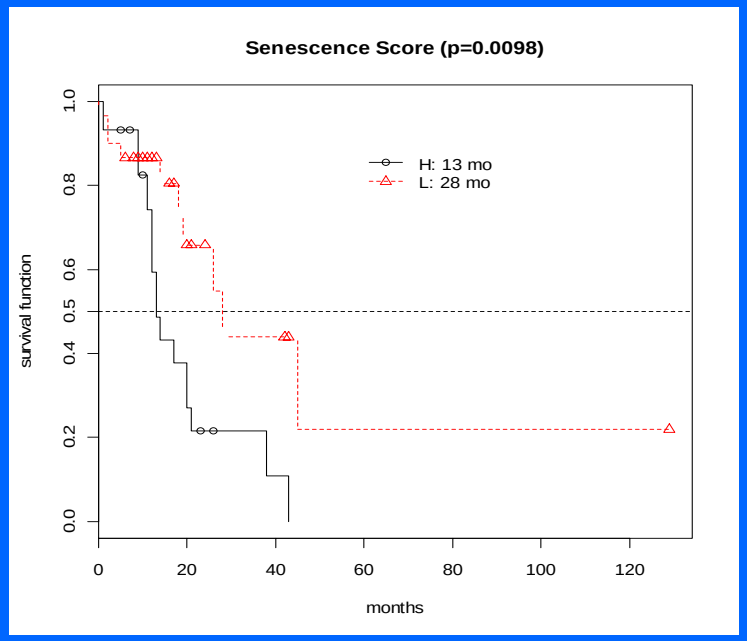
The Moffitt Total Cancer Care Protocol (TCCP) (www.moffitt.org/totalcancercare) is a study that allows the prospective acquisition of tissues from patients undergoing cancer procedures at Moffitt or a TCCP-collaborating site. The goal of the study is to link molecular profiling, histopathological, and clinical data to discover and translate personalized medicine. All patients provide informed consent.

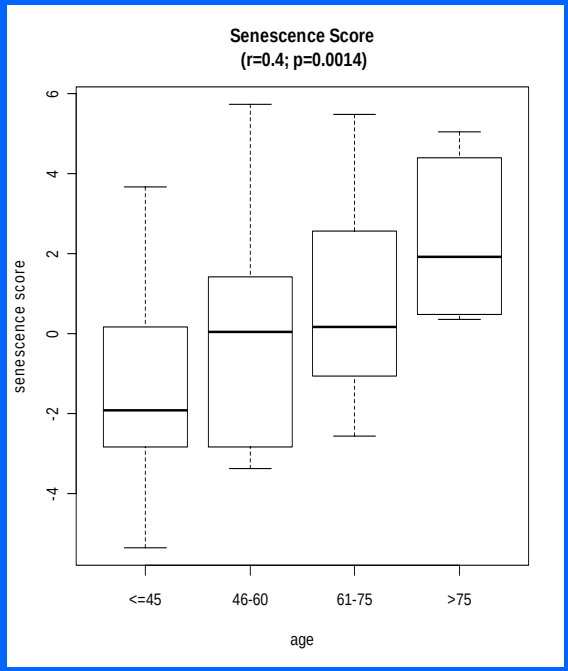
Material and Methods.

Between 2006 and 2010 approximately 18,000 well annotated fresh tumor samples were collected, macro-dissected and arrayed. The samples were arrayed on a custom version of the Affymetrix HG-U133 GeneChip. These tumors included 150 brain tumors, and of these, 60 were gliomas (patients ages 32 to 88). A set of 14 known senescence-associated genes (SAGs) including CCL2, CCL7, CDKN1A, COPG, CSF2RB, CXCL1, ICAM1, IGFBP3, IL6, IL8, SAA4, TNFRSF11B, TNFSF11 and TP53 were the focus of the study (1). An overall senescence score was generated using principal component analysis. Pearson correlation and Cox proportional hazards regression were used to examine the association of each SAG and the senescence score with age at onset and overall patient survival. False discovery rate (fdr) was used to adjust for multiple comparisons.

Results:

We found an age-related gradient in the senescence score representation of the combined SAGs (r = 0.40; p=0.0014). Ten SAGs were significantly correlated with age (false discovery rate at 5%): IGFBP3 (r=0.44), ICAM1 (r=0.40), IL6 (r=0.38), CDKN1A (r=0.35), TNFSF11 (r=0.34), TP53 (r=0.34), CXCL1 (r=0.31), CCL7 (r=0.30), COPG (r=0.29), and CSF2RB (r=0.29). The SAG signature was also correlated with poor prognosis (p=0.0098; median survival: 13 and 28 months, respectively, for high versus low senescence score). Two SAGs were significantly associated with patient survival: IL6 (14 versus 38 months) and COPG (13 versus 38 months).





Conclusions:

We report for the first time an SAG signature in HGG associated with age at onset and patient outcome. This signature composed of genes involved in cell cycle regulation, apoptosis, cell proliferation, and angiogenesis may define a more aggressive subtype of high-grade glioma.

Reference:

1. Campisi J. et al. PLoS Biology, 2008).