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Authors
Kesari, Santosh
Bota, Daniela A

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Fos-related antigen-1 (Fra-1) is a regulator of glioma cell malignant phenotype

Santosh Kesari1 and Daniela A. Bota2-4,*

1Department of Neurosciences; Moores Cancer Center; University of California, San Diego; La Jolla, CA USA; 2Departments of Neurology and Neurological Surgery; University of California, Irvine Medical Center; and 3Chao Family Comprehensive Cancer Center; University of California, Irvine; School of Medicine; Irvine, CA USA

Malignant gliomas are aggressive cancers, characterized by innate resistance to therapies and short patient survival. However, the prognosis of these tumors is changing, with the advent of molecular-targeted therapies aimed at the oncogenic signaling associated with tumor specific proliferation, invasion and angiogenesis pathways. There is renewed hope that the unprecedented amount of basic science knowledge acquired in recent years will translate into improved clinical outcomes.

AP-1 (activating protein-1) is a collective term referring to dimeric transcription factors composed of Jun, Fos or ATF (activating transcription factor) subunits that bind to a common DNA site, the AP-1-binding site. There is a high level of complexity in the dimer’s formation, as pairing can consist of both homodimers and heterodimers of Jun (v-Jun, c-Jun, JunB, JunD), Fos (v-Fos, c-Fos, FosB, Fra-1, Fra-2) or activating transcription factor (ATF2, ATF3/LRF1, B-ATF) bZIP (basic region leucine zipper) proteins. In addition, the heterodimers display distinguishable DNA binding specificities from each other and from their parental homodimers, raising the question of the different biological functions each and every one of these dimers play both in normal physiology and in the pathophysiology of human diseases. AP-1 has been implicated in a large variety of biological processes including cell differentiation, proliferation, apoptosis and oncogenic transformation.

AP-1 activity is modulated by interactions with other transcriptional regulators and is further controlled by upstream kinases that link AP-1 to various signal transduction pathways.

AP-1 is constitutively activated in glial tumors, and directly associates with resistance to chemotherapy, and decreased response to apoptotic signals. Malignant gliomas have an abundance of AP-1 stimulating signals, including epidermal growth factor receptor, and platelet-derived growth factor receptor, and contain mutations in the p53 gene, which contribute to phosphoinositide-3-kinase (PI3K)/Akt and Ras/mitogen-activated protein kinase activation. PTEN (phosphatase and tensin homologue deleted on chromosome ten), a tumor suppressor gene commonly inactivated in glioblastoma, downregulates AP-1, while aberrant PTEN expression contributes to AP-1 constitutive activation.

Interestingly, curcumin, a naturally occurring polyphenol derived from the root of the rhizome, *Curcuma longa*, inhibits AP-1 activation and sensitizes glioma cells to several clinically utilized chemotherapeutic agents (cisplatin, etoposide, camptothecin and doxorubicin) and radiation.

The members of Fos protein family are subdivided in two main groups according to their ability to transform rodent fibroblasts: transforming (c-Fos, FosB) and non-transforming (Fra-1 and Fra-2). Fra-1 (also named FOSL1), albeit unable to transform, is involved in the malignant progression of multiple tumor types, including non-small cell lung carcinoma and colorectal carcinoma. Silencing or knockdown of Fra-1 expression reverses...
anti-vascular endothelial growth factor (VEGF) antibody has obtained accelerated FDA approval for the treatment of recurrent glioblastoma (GBM). In this context, VEGF-D, the most recently described member of the VEGF family, has an important role to play. Previously, Debinski et al. have shown that VEGF-D is ubiquitously expressed in GBM under the tight regulation of Fra-1, which in turn activates VEGF receptors 2 and 3, which are very important for tumor angiogenesis. This was the initial report that Fra-1 is a potential novel target for malignant gliomas.

Jun B is an essential gene for the normal embryonic development. In trophoblasts, the lack of JunB causes a deregulation of proliferin, matrix metalloproteinase-9 (MMP-9) and urokinase plasminogen activator (uPA) gene expression, resulting in a defective neovascularization of the decidua and subsequent death of embryos. Jun B involvement in cancer, however, is more complicated as it seems that it can both promote and hinder carcinogenesis. JunB is amplified or overexpressed in cervical cancer cell lines and in tumor samples from patients with primary cutaneous T-cell lymphomas. However, Jun B can also suppress tumorigenesis and can maintain replicative senescence as a balance against excessive proliferation and carcinogenesis. The preferential association of Fra-1 and Jun B was shown to be related with malignant transformation of JB6 epithelial cells, with gain of JunB and Fra-1 binding complexes in all transformed cells, which might contribute to a more proliferative phenotype. The heterodimer Fra-1-JunB is able to regulate the expression of multiple genes including the interleukin 2 (IL-2), and cyclin A, which in turn promote neoplastic cell growth and proliferation.

In the last issue of Cancer Biology & Therapy, Debinski and Gibo present their research work showing that the Fra-1-JunB partnership is maintained in glioma, and that this heterodimer binds to the AP-1 site in the JunB promoter. Their interest on the Fra-1-JunB interaction stems from their previously published work, where they document that JunB is 7-fold overexpressed in response to ectopic Fra-1 expression in H4 malignant glioma cells. Such
efforts to clarify the AP-1 interactions in malignant glioma might ultimately elucidate the importance of this pathway in gliomagenesis and create the ability to find a therapeutic target that can affect multiple cancer processes such as vascularization, migration and proliferation.

The authors use multiple, elegant techniques to highlight the important characteristics of this interaction. First, with the use of shRNA and siRNA, they show that Fra-1 silencing depletes cells of extended cellular processes and impairs cell migration, suggesting that Fra-1 plays an important role in glioma invasion in the brain. These morphologic changes were not fully replicated with JunB knock-down, suggesting that the two genes do not have identical functions in glioma cells.

The most important contribution is the elucidation of the Fra-1 and JunB interaction at both protein and gene levels. By employing Fra-1 immunoprecipitation, a significant increase of JunB was noted. The Fra-1-JunB complex is not the only AP-1 heterodimer detected, as c-Jun and JunD were also detected in the cell lysate. Almost all the immunoreactive Fra-1 was phosphorylated, which is the modification required for complex formation. A similar finding was demonstrated for JunB.

Chromatin immunoprecipitation of the AP1 binding sites on the junB promoter resulted in both Fra-1 and Jun-B precipitation on the AP-1 canonical site, and only of JunB on the noncanonical site. This is another proof of the intricacy of AP-1 regulated mechanisms, as Fra-1 can regulate JunB in cooperation with JunB, but JunB can also transactivate itself.

A few unsolved questions will need further scientific inquiry. First and foremost, we are still to determine the roles of the different Fra-1 heterodimers in malignant glioma. We now know more about the interaction with JunB, but the importance of Fra-1 interactions with c-Jun and JunD are unknown. If different complexes have different functions—and possibly some of them promote oncogenesis while some others inhibit it—we still need to determine how to affect this fine balance in order to identify potential drug targets. Secondly, the gene targets of Fra-1-JunB in malignant glioma remain to be determined: multiple genes were shown to be potential targets for the AP-1 complexes in both embryogenesis and in cancer—and the targets differ between different malignancies. However, the Fra-1-JunB downstream targets are still elusive in gliomas.

The holy grail of glioma therapy is to find a potent, targeted treatment. Inhibition of multiple molecular pathways seemed promising in vitro and in animal models. However, many of them failed to improve patients survival. As curcumin—an AP-1 inhibitor seems to hold initial promise, it would be interesting to be able to develop specific compounds targeted to Fra-1 and other important AP-1 proteins. This avenue of research might permit further refinements of our approaches to an almost universally deadly disease.

References