**Editorial**

**Soluble Fas and Cancer**

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Recent studies have revealed an anticipated link between a soluble receptor antagonist for the proapoptotic protein Fas and cancer. In this issue, Ugurel et al. (1) demonstrate that sFas 2 levels correlate with poor prognosis and decreased overall survival in patients with melanoma. On the basis of available evidence, it appears that nonhematopoietic tumor development and progression may represent a continuum where Fas expression and/or function are progressively lost on the malignant cell. Fas loss-of-function has been shown to enhance tumor frequency, decrease tumor latency, and increase spontaneous tumor metastasis in several experimental models (2–4). Production of sFas in tumor patients may be a key mechanism to inhibit Fas-mediated apoptosis. The identification of sFas levels as a predictor of outcome in malignant disease further establishes a connection between Fas loss-of-function and tumor progression that is poised for detailed exploration.

Transduction of the Fas apoptotic signal requires trimerization of membrane-associated Fas, an intact DISC signaling complex, and the absence of high levels of cell-associated inhibitory or antiapoptotic proteins such as FAP-1, FAIM, Toso, c-FLIPP, bcl-2, and bcl-Xl. Trimerization of Fas receptor can be inhibited by soluble receptors that act as decoys, binding FasL and preventing association with transmembrane Fas. To date, two distinct soluble receptors, designated sFas and DcR3, have been shown to bind FasL and competitively antagonize Fas signaling (5–8). sFas is the designation given to multiple soluble isoforms of the Fas protein lacking the transmembrane region of Fas. DcR3 is a decoy receptor superfamily, sFas is generated from alternative mRNA splicing instead of proteolytic cleavage of membrane-associated protein. To date, five distinct isoforms of sFas have been described. The most predominant isoforms result from an in-frame deletion of the transmembrane domain, resulting in a loss of membrane anchoring. The molecular controls that regulate alternative sFas splicing have not been elucidated. Understanding these controls may be especially important in manipulating sFas levels in malignant disease.

Our laboratory originally documented that sFas was increased in the serum of cancer patients in a manner directly related to tumor stage and burden, suggesting a potential role for sFas in the biology of malignant disease (9). Since that time other laboratories have documented that sFas levels are increased in hepatocellular carcinoma, bladder, breast, ovarian, renal cell carcinoma, and now, melanoma (1, 10–14). The fact that increased sFas levels are correlated with poor prognosis in melanoma is particularly interesting because we have shown that loss of Fas-mediated apoptosis can enhance melanoma lung metastasis using a mouse model (4). Taken together, these data predict a causal role for sFas in melanoma progression. Indeed, sFas production may provide a key protective signal that helps tumor cells avoid apoptosis in their hostile microenvironment. In this regard, it is particularly notable that Fas-induced tumor apoptosis has also been implicated recently in immune surveillance (2, 3). As the pathophysiological roles for sFas emerge in malignant disease, this antagonistic, antiapoptotic protein may well become a new target in both detection and intervention. In melanoma, for example, sFas levels may prove to useful to predict those thin melanomas likely to progress, as well as in the selection of therapeutic strategies.

**References**


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*Clin Cancer Res* 2001;7:1108-1109.

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