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FADD the bad in head and neck cancer

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It has been known for many years that the protein Fas-associated death domain (FADD) is an essential protein forming the apical portion of the extrinsic apoptosis pathway that permits association of death receptors, e.g., CD95, DR4, DR5 with pro-caspases 8 and 10, thereby facilitating caspase activation (e.g., ref. 1, and references therein). It is also known that FADD can recruit other proteins to regulate NFκB and MAPK pathways which in turn can promote proliferation and cell cycle progression. In NSCLC high expression of FADD has been associated with shorter survival times and lymph node metastasis or oral cancer and worse survival, and the present manuscript in head and neck cancer demonstrates similar findings with respect to lymph node metastasis and survival.[2,3]

The authors of the present study had previously shown that high expression levels of DR5, caspase-8 or both proteins correlated with a poorer prognosis of patients with lymph node metastasis.[4] Elevated expression of caspase-8 correlated with a prolonged tumor response in patients who did not have lymph node spread. The present studies showed a strong correlation for FADD/Caspase 8/DR5 expression in metastatic and non-metastatic tumor cells. For non-metastatic tumors high FADD/caspase 8/DR5 levels correlated with survival whereas in metastatic tumors high FADD/Caspase 8/DR5 levels correlated with reduced survival. The question still remains as to how enhanced FADD signaling could promote tumor progression in this cancer type: no additional studies were performed in the present manuscript to examine possible changes in cell signaling, e.g., ERK, JNK, NFκB in these cells that could be correlated with altered FADD levels.

If elevated ERK, JNK, and NFκB signaling is present in FADD high tumor cells a number of rational drug treatments could be proposed to reduce the impact of FADD overexpression. For example, Velcade is a clinically relevant inhibitor of NFκB function and multiple MEK1/2 inhibitors are under advanced clinical development.[5] As such, it will be of interest to see in the future whether rationally based combination therapy trials will be proposed by these or other investigators for the treatment of this form of head and neck cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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