

Oncogenic Ras triggers cell suicide through the activation of a caspase-independent cell death program in human cancer cells.

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To prevent neoplasia, cells of multicellular organisms activate cellular disposal programs such as apoptosis in response to deregulated oncogene expression, making the suppression of such programs an essential step for potentially neoplastic cells to become established as clinically relevant tumors. Since the mutation of ras proto-oncogenes, the most frequently mutated proto-oncogenes in human tumors, is very rare in some tumor types such as glioblastomas and gastric cancers, we hypothesized that mutated ras genes might activate a cell death program that cannot be overcome by these tumor types. Here we show that the expression of oncogenically mutated ras gene induces cellular degeneration accompanied by cytoplasmic vacuoles in human glioma and gastric cancer cell lines. Cells dying as a result of oncogenic Ras expression had relatively well-preserved nuclei that were negative for TUNEL staining. An immunocytochemical analysis demonstrated that the cytoplasmic vacuoles are derived mainly from lysosomes. This oncogenic Ras-induced cell death occurred in the absence of caspase activation, and was not inhibited by the overexpression of anti-apoptotic Bcl-2 protein. These observations suggested that oncogenic Ras-induced cell death is most consistent with a type of programmed cell death designated 'type 2 physiological cell death' or 'autophagic degeneration', and that this cell death is regulated by a molecular mechanism distinct from that of apoptosis. Our findings suggest a possible role for this non-apoptotic cell death in the prevention of neoplasia, and the activation of the non-apoptotic cell death program may become a potential cancer therapy complementing apoptosis-based therapies. In addition, the approach used in this study may be a valuable way to find genetically-regulated cell suicide programs that cannot be overcome by particular tumor types.

PMID: 10327074 [PubMed - indexed for MEDLINE]