Mechanism for elimination of a tumor suppressor (3): aberrant splicing (6) of a brain (1)-specific exon (1) causes loss of function of Bin1 in melanoma (5). Loss of tumor suppressors that restrain important oncoproteins (3) such as c-Myc (3) may contribute to malignant progression (6). Bin1 is an adapter protein with features of a tumor suppressor that was identified through its interaction with and inhibition of the oncogenic properties of c-Myc. In this study, we analyzed the patterns of Bin1 expression in normal melanocytes (1) and melanoma cells (1) at different stages of tumor progression (6). Evidence is provided that Bin1 function is abrogated in melanoma cells by a mechanism based on aberrant splicing of a tissue-specific exon. Specifically, most melanoma cells inappropriately expressed exon 12A (1), which is spliced alternately into Bin1 isoforms (11) found in brain but not into isoforms found in melanocytes and many other nonneuronal cells (1). Exon 12A sequences abolished the ability of Bin1 to inhibit malignant transformation (6) by c-Myc or adenovirus E1A (7). Similarly, these sequences abolished the ability of Bin1 to induce programmed cell death (6) in melanoma cells that endogenously expressed exon 12A. Our findings suggest that aberrant splicing of Bin1 may contribute to melanoma progression (6), and they define a mechanism by which the activity of a tumor suppressor can be eliminated in cells.