PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Inactivation of the apoptosis effector Apaf-1 in malignant melanoma

ArticleInfo		
ArticleID	:	110
ArticleDOI	:	10.1186/ar-2001-66884
ArticleCitationID	:	66884
ArticleSequenceNumber	:	67
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2001–2–15 OnlineDate : 2001–2–15
ArticleCopyright	:	Biomed Central Ltd2001
ArticleGrants	:	
ArticleContext	:	130753311

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Keywords

Apaf-1, Apoptosis, p53

Context

Apoptosis is an important mechanism limiting cellular expansion in situations of excessive cell growth such as neoplasia or chronic inflammation. Mitochondria play a key role in stress induced apoptosis and provide an amplification loop of death receptor triggered apoptotic signals. The release of mitochondrial cytochrome c into the cytosol is a critical event in apoptosis. Cytochrome c activates oligomerization of apoptotic protease activating factor-1 (Apaf-1), an adapter protein that links the mitochondrial signal to activation of caspase-9, an enzyme involved in apoptosis. Inactivation of apoptosis signaling pathways as a result of mutations or epigenetic mechanisms has been demonstrated in cancer, autoimmunity, and in the pseudotumoral growth of rheumatoid synovium.

Significant findings

In malignant melanoma cell lines retaining functional p53 protein, the authors identified a novel mechanism of apoptotic resistance: functional loss of Apaf-1 protein. They found a high rate of allelic loss in the Apaf-1 locus leading to low or undetectable levels of Apaf-1 mRNA and protein. This inactivation was not due to deletions or other loss-of-function mutations of Apaf-1 gene. They also excluded gene silencing by direct methylation of the Apaf-1 promoter and suggested that this shutdown of Apaf-1 expression could be due to methylation of transactivating elements. Lack of Apaf-1 protein made melanoma cells insensitive to apoptosis mediated by p53, adenoviral E1A, and Bax. In contrast, ectopic expression of Apaf-1 in deficient cells restored apoptosis susceptibility of these cells.

Comments

The novel molecular defect leading to defective p53-mediated apoptosis in cancer cells increases the spectrum of proteins critically involved in apoptotic regulation. This finding is particularly relevant to

the study of potential abnormalities of apoptotic control in the process of hyperplasia and pseudotransformation of rheumatoid synovium. Rheumatoid fibroblasts exhibit defective or inappropriate apoptotic responses to various stimuli. However, p53 mutations and other apoptotic defects are only inconsistently found in these cells, suggesting that additional abnormalities could be involved. The identification of acquired defects leading to abnormal expression of Apaf-1 provides a novel area of research relating to chronic diseases characterized by apoptosis resistance.

Methods

PCR, *in situ* hybridization, western blot, northern blot, adenovirus-mediated gene transfer

References

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