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Review

Correlation between P53 expression and malignant risk of gastrointestinal stromal tumors: Evidence from 9 studies

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Abstract

Purpose: The published data about p53 expression and its potential value in malignant risk of Gastrointestinal Stromal Tumors patients seemed inconclusive. To derive a more precise estimation of the relationship between p53 and Malignant risk of GIST, a meta-analysis was performed.

Materials and methods: Studies have been identified by searching PubMed and Embase. Inclusive criteria were GIST patients, evaluation of p53 expression and malignant risk. The odds ratio (OR) for positive rate of p53 in NIH very low risk group vs. NIH low risk group, the odds ratio (OR) for positive rate of p53 in NIH low risk group vs. NIH Intermediate risk group and the odds ratio (OR) for positive rate of p53 in NIH Intermediate group vs. NIH high risk group were calculated with 95% confidence interval (CI) for each study as an estimation of potential value of p53 in malignant risk of GIST.

Results: A total of 9 studies including 768 patients were involved in this meta-analysis. The meta-analysis of positive rate of p53 in NIH VL group vs. NIH L group did not attain significant difference (OR 0.38 95% CI, 0.11–1.28; $P = 0.12$ $P_{\text{heterogeneity}} = 0.51$). However the overall OR for positive rate of p53 in NIH L group vs. NIH I group revealed that significantly elevated risks of positive p53 in NIH I group were achieved (OR 0.44 95% CI, 0.24–0.82; $P = 0.009$ $P_{\text{heterogeneity}} = 0.32$). The overall OR for NIH I group vs. NIH H group was 0.62 (95% CI, 0.37–1.02; $P = 0.06$ $P_{\text{heterogeneity}} = 0.25$).

Conclusion: The results indicate p53 overexpression correlate with the malignant risk increasing of GIST and have a primary and closest relationship within the NIH I risk group of GIST.

Keywords: Gastrointestinal stromal tumors; Immunohistochemistry; P53; Malignant risk; Meta-analysis

Introduction

Gastrointestinal stromal tumor (GIST) is a rare tumor of the gastrointestinal tract but the most common primary mesenchymal tumor of the gastrointestinal tract.[1] GIST expresses the tyrosine kinase receptor KIT, which is the protein product of the KIT protooncogene. GIST is generally characterized by gain-of-function mutations of KIT.[2] Moreover, recent studies have described the mutations of PDGFRA in some populations of GIST.[3,4] KIT or PDGFRA mutations may result in the constitutive activation of signaling, which leads to uncontrolled cell proliferation and resistance to apoptosis. However 12% of GIST cases exist without any mutations of either KIT or PDGFRA. The mechanism of GIST genesis is not fully understood. To our knowledge, GIST has a wide spectrum of biologic behavior ranging from benign to malignant. Because of its specific biologic behavior, there is not a standard definition of benign and malignancy when a patient is diagnosed at the early stage of GIST. According to the consensus approach at the National Institutes of Health (NIH) in 2001, they have recommended the use of risk assessment in predicting GIST behavior, in preference to trying to draw a sharp line between benign and malignant lesions. They categorized GIST into 4 groups: very low risk, low risk, intermediate risk, and high risk (Table 1).[5] Although this

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Table 1
National Institutes of Health system of risk grading for GIST.

	Tumor size (cm)	Mitotic count
Very low risk	<2	≤5/50HPF
Low risk	2–5	≤5/50HPF
Intermediate risk	≤5	>5 to ≤10HPF
	>5 to ≤10	≤5/50HPF
High risk	>5	>5/50HPF
	>10	Any mitotic rate
	Any size	>10/50HPF

system is useful to predict GIST behavior, it is only based on the assumption by a wide range of experts on GIST. To explore the internal molecular incidences that cause the increase of malignant risk, several studies were designed concerning cell-cycle regulatory proteins (CCRP).

It has been proved that constitutive KIT/PDGFR activation promotes proliferation and inhibits apoptosis of neoplastic cells by CCRP signaling pathway (Fig. 1). And the alteration of CCRP is often implicated in the pathogenesis and tumor progression of various kinds of tumors. Among these cell-cycle proteins, p53, as a cross-talk regulator, play a key role in both cell-cycle and apoptosis control.[18]

As in other neoplasms, we hypothesize that p53 genetic aberration in GIST may be important in malignant transformation and be significant in predicting patient prognosis, particularly because it is known that when the genome is damaged, p53 suppresses the cell growth cycle by activating the transcription of genes that cause arrest in the G1 phase. This regulatory function may be lost in most neoplasms which have p53 overexpression and GIST is no exception.

In normal cells, the p53 protein level is low. Several studies revealed the fact that p53 were more frequently seen in the aggressive group than in the none-aggressive GIST group, indicating that p53 were highly correlated with the biological behavior of GIST.[27,29,30] Therefore, a number of studies have been designed to test the relationship between p53 and malignant risk of GIST, with conflicting results partially because of the relatively small sample size in each of published studies. Therefore we performed a meta-analysis of the published studies to derive a more precise estimation of the association.

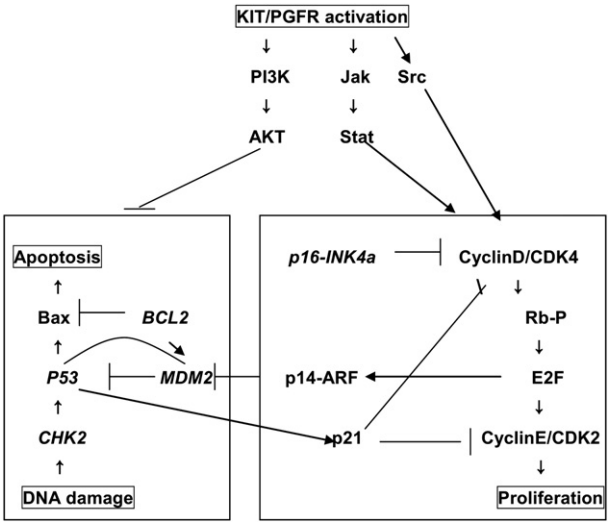

Figure 1. KIT/PDGFR mutation activates signaling pathway: proliferation and apoptosis.

Materials and methods

Publication search

Two electronic databases (PubMed and Embase) were searched (last search was updated on 24 September 2011, using the search terms: 'gastrointestinal stromal tumor' and 'p53'). All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand-searched to find additional eligible studies. Only published studies with full-text articles were included. When more than one of the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis.

Inclusion criteria

The inclusion criteria were as follows: (a) evaluation of the p53 expression in GIST and biologic behavior; (b) NIH risk study; and (c) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

Data extraction

Information was carefully extracted from all eligible studies by two of the authors (Zong L and Chen P), according to the inclusion criteria listed above. The following data were collected from each study: first author's surname, publication date, category method, total number of NIH very low risk group, low risk group, intermediate risk group and high risk group, and number of positive p53 in each risk group of NIH, respectively. We did not define any minimum number limit of patients to include a study in our meta-analysis.

Statistical analysis

Odd ratios with 95% CI were used to assess the predictive value of p53 expression in malignant risk of Gastrointestinal Stromal Tumors, according to the method of Woolf. Heterogeneity assumption was checked by the χ^2-based Q-test. A P-value greater than 0.10 for the Q-test indicates a lack of heterogeneity among studies, so the OR estimate of the each study was calculated by the fixed-effects model (the Mantel–Haenszel method). Otherwise, the random-effects model (the DerSimonian and Laird method) was used. The significance of the pooled OR was determined by the Z-test and $P > 0.05$ was considered as statistically significant. Sensitivity analyses were carried out to check if