Interrelationship of serum S100B and P53 in brain tumour patients

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Abstract

The interrelationship of serum S100B and P53 concentrations and their association with tumour type and size in patients was determined. S100B and P53 concentrations were measured in serum of patients and normal healthy volunteers. Serum S100B concentrations were significantly higher in patients (mean 50%) than in healthy controls (p< 0.001). P53 concentrations were elevated only in five patients (mean 28%). No significant correlation was found between S100B and P53. Significant positive correlation was observed between S100B concentration and large tumour size (p< 0.05) but not with small tumours. Similarly,there was no significant correlation between P53 concentrations and tumour size.Heterogeneity of S100B expression exists in brain tumours. However, S100B was also found to be pituitary-specific. High serum concentration of P53 was found in five patients with large tumour. These findings warrant further larger clinical studies for better understanding the interrelationship of these serum makers and the development and/or progression of these malignancies.

Keywords: S100B, P53, brain tumours, interrelationship of biomarkers.

Introduction

S100B protein has been found in a variety of other nervous tissues, which is present in serum of healthy individuals at very low concentrations. Increased expression of S100B protein has also been found in a range of human tumours.[1,2] Although the functional role of S100B in carcinogenesis is still not fully understood, several studies have demonstrated that the elevated levels of this protein play a role in cell proliferation by down regulating P53 protein.[1]

P53 is a key tumour suppressor protein, and is present in the serum at very low concentrations. Recent studies have shown that S100B interacts directly with P53 protein and binds to its trans-activation domain as well as its C terminal end, which results in decrease in the P53 level and loss of its tumour suppressing activity.[3] This S100B-P53 protein-protein interaction complex is cell specific and affects specific cellular functions including suppression of P53-dependent target genes such as HDM2, P21 and c-BCL2. Moreover, elevated levels of S100B may also block post-translational modifications of P53in the cell which could also contribute to P53 down regulation[4] resulting in increased risk of malignant transformation and tumour genesis.

Methods and Results

Measurement of serum concentration S100B and P53 was performed on eighteen patient samples as described in our previous study.[5] The study was carried out at Neurosurgical Ward, Jinnah Postgraduate Medical Centre. Karachi, from May 2007 to April 2008. Only those patients were included in this study, who did not receive any chemotherapy or radiotherapy. Patients with CNS metastases and other serious non-malignant co-existent disease were excluded. They underwent initial computed tomography (CT) and magnetic resonance imaging (MRI) and were diagnosed with different types of brain tumours. Pathologies included five gliomas, five meningiomas, two pituitary tumours, one ependymoma, one arteriovenous malformation (AVM), one lymphoma, one medulloblastoma, one acoustic neuroma and one orbital neuroblastoma. The serum concentrations of S100B and P53 were measured using chemiluminescence-immunometric assay (CIA) and enzyme-linked immunosorbent assay (ELISA), respectively. Experimental data were statistically analysed using Mann-Whitney and Spearman's rank correlation tests.

All normal healthy subjects had serum S100B concentrations within the reference range (0.00-0.15 µg/L). The mean concentrations of S100B in patients with small and large tumour were 0.17 and 0.21 µg/L, respectively. However, the overall mean concentrations were 0.19 ± 0.12 ?g/L (range 0.09 - 0.60). The serum S100B concentrations were significantly higher (p < 0.001) in patients with brain tumours than in healthy controls. Elevated concentrations were observed in meningioma (3/5), glioma (2/5) and Acoustic Neuroma (1/1) Pituitary tumour 2/2 Medulloblastoma (1/1).All other patients had

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serum S100B concentrations within the reference range i.e. < 0.15 µg/L.

The mean concentrations of P53 in serum of normal healthy subjects were 30.6 ± 3.8 pg/mL (range 28.4-35.0) while in patients 37.9 ± 30.0 pg/mL (range 13.4-112.0). However, the mean concentrations of P53 in patients with small and large tumours were 27.2 and 54.7 pg/mL, respectively. No statistically significant difference was found between the P53 concentrations in serum of healthy controls and patients with brain tumours. Elevated concentrations were observed in meningioma (3/5, glioma (1/5) and ependymoma (1/1). All other patients (pituitary tumours, medulloblastoma, lymphoma, acoustic neuroma, and neuroblastoma) had less than the mean P53 concentration of normal subjects.

Out of 18 brain tumour patients, 11 had small tumours (< 50 cm^3) while 7 patients had larger tumours (> 50 cm^3). Poor correlations were found between S100B and tumour size. However, a significant positive correlation was observed between S100B concentration and large tumour size (p< 0.05) but not with small tumours.Similarly there was poor correlation between P53 concentrations and tumour size. No statistically significant correlations were found between S100B protein and P53 concentrations in serum of patients with small and large tumours. However, the mean concentrations of S100B and P53 were higher in patients than the mean concentrations of normal subjects.

Discussion

In various human tumours, clinical decision-making is based on radiological or/and histopathological findings. Biomarkers are used in clinical practice in order to support a diagnosis, or monitor the progression of a disease by measuring their concentrations in serum. This is the first study that has measured the concentrations of S100B and P53 in serum of patients with brain tumours and attempted to inter-correlate their concentrations.

Out of five meningiomas patients three showed elevated serum S100B concentrations, i.e. > 0.15 µg/L and had large tumours (> 50 cm^3). Interestingly, one meningioma patient had an exceptional 5 fold increase in S100B concentrations over the mean concentration in normal subjects. Our results are consistent with those of previous studies, which showed that patients with larger tumour size had elevated postoperative serum S100B concentrations, suggesting these patients had a 9-fold greater risk of neurological deterioration.[6] Also, highly elevated concentrations of P53 were observed in three meningiomas patients with larger tumour size (> 50 cm^3). The serum P53 concentrations in these meningioma

patients (3/5) were 2-3 fold higher than the mean concentration of normal subjects while other meningioma patients (2/5) showed less than the mean concentration of normal subjects. The earlier findings also showed higher expression of P53 in meningioma patients using an immune-staining method.[7]

Elevated serum S100B concentrations (> 0.15 µg/L) were found in two patients with pituitary tumour. Two out of five glioma patients had elevated serum S100B concentrations, consistent with the results of a previous study that demonstrated a high plasma concentration of this protein in Malignant gliomas patients.[8] One of the patients diagnosed with medulloblastoma had elevated serum concentration of S100B. This patient, who died a week after surgery, also had a 2-fold increased pre-operative serum concentration of S100B. The patients who were diagnosed with ependymoma and lymphoma had serum S100B concentrations within the normal range i.e. < 0.15 µg/L, while in a patient with acoustic neuroma, the serum concentration was above the normal range. This study demonstrated no statistically significant correlations to be found between S100B protein and P53 concentrations in serum of patients. Previous studies have demonstrated a direct correlation between S100B and P53 proteins at the cellular level[1] while other studies reported a lack of correlation.[9] Our results also indicate no direct correlation between the steady-state concentrations of these proteins.

This lack of correlation does not negate the role of these proteins in the control of transcription of each other, as previously described.[1,4,9] This is because the steady states of both the RNA and proteins are affected not only by the rate of synthesis, but also product stability and degradation,[10] and are influenced by a range of interactions with other regulatory pathways in the cell. In cases where the P53 concentration exceeds a certain set point, the tumour suppressor protein contributes to its own inactivation by up-regulating the transcription of not only HDM2, but also S100B. This may be due to an increasing concentration of S100B on the one hand and deactivation of P53 activity due to mutation and down-regulation by S100B on the other hand during tumour development. Considering the above, it was difficult to differentiate various possible causes of the lack of correlation between S100B and p53 protein in the serum of studied patients.

Conclusion

Heterogeneity of S100B expression exists in brain tumours. High serum concentration of P53 in five patients with large tumour may indicate that this tumour

suppressor was in a mutant form since in most cancers, non-mutational P53 over-expression is considered rare. It is conceivable that measurement of S100B and P53 in serum could become a routine test for prognosis for these brain cancers. However, these findings warrant further larger clinical studies to investigate the potential role and relevance of these biomarkers to the disease process and prognosis.

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