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Expression of metallothionein (MT) and gluthatione s-transferase pi (SGTP) in the bone marrow of patients with myeloproliferative disorders (MPD)

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Overexpression of SGTP and/or MT may contribute to various carcinogenic processes and to resistance to anticancer treatment. The importance of these proteins, although clearly established in solid tumours, has not been fully understood in haematopoietic neoplasm. The aim of this study was to determine the expression of MT and SGTP in the bone marrow of patients with MPD. Twenty paraffin-embedded bone marrow core biopsy specimens from newly diagnosed patients with MPD were evaluated — osteomyelofibrosis (OMF), n = 9 and chronic myelocytic leukaemia (CML), n = 11. We demonstrate increased SGTP and MT expression in the bone marrow of MPD patients. In our study levels of MT in OMF patients were higher than in CML. This suggests that MT expression may correlate with bone marrow fibrosis. These data, although based on a relatively small number of patients, raise the possibility that SGTP and MT may play a role in the pathogenesis of MPD. The clinical significance of this phenomenon needs further investigation.

Key words: metallothionein, gluthatione s-transferase pi, myeloproliferative disorders

INTRODUCTION

Metallothionein (MT) is low molecular weight cysteine-rich protein, which has the ability to bind and sequestrate heavy metal ions such as zinc, copper, cadmium and mercury. MT plays an important role in the detoxification of toxic metals and probably in cellular protection against ionising radiation and cytotoxic drugs [9]. Gluthatione s-transferase pi (SGTP) belongs to a family of detoxification enzymes. Malignant tumours often contain increased amounts of SGTP [10]. Myeloproliferative disorders (MPD) are clonal diseases originating in a pluripotential haematopoietic stem cell. MPD are characterised by abnormally high levels of cells of particular haematopoietic cell lineage. The clinical course and management differ among the various disorders. MPD include chronic myelogenous leukaemia (CML), polycythaemia vera (PV), essential thrombocythaemia (ET), and myelofibrosis with myeloid metaplasia (OMF) [3, 7].

MT and SGTP overexpression has been found in various solid tumours [1, 4, 5, 10]. There are limited

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data concerning the role of MT and SGTP in haematological malignancies. The aim of this study was to determine the expression of MT and SGTP in the bone marrow of patients with MPD.

MATERIAL AND METHODS

20 paraffin-embedded bone marrow core biopsy specimens from patients newly diagnosed with MPD were evaluated — osteomyelofibrosis (OMF), n = 9 and chronic myelocytic leukaemia in the chronic phase (CML), n = 11. The OMF was diagnosed according to Polycytaemia Vera Study Group criteria. The diagnosis of CML was confirmed by the presence of the Philadelphia chromosome and/or BCR-ABL oncogene [3, 7].

Bone marrow sections were stained immunohistochemically for MT and SGTP. The samples under examination were fixed in 10% buffered formalin and then embedded in paraffin. The preparations were stained with haematoxylin and eosin and evaluated histopathologically. The deparaffinised sections were incubated with mouse monoclonal antibodies against MT and SGTP (Dako, Denmark). At the next step streptavidin-biotinylated peroxidase (LSAB2, Dako, Denmark) complex was used and the activity of the latter was evaluated using DAB (Dako, Denmark). In each case the negative control was included with Primary Negative Control (Dako, Denmark) and then — LSAB2 and DAB.

RESULTS AND DISCUSSION

The results of SGTP and MT expression are summarised in Figures 1 and 2.

Overexpression of SGTP and/or MT may contribute to various carcinogenic processes and to resistance to anticancer treatment. The importance of these proteins, although clearly established in solid tumours, has not been fully understood in haematopoietic neoplasms. In acute myelocytic leukaemias the gene encoding SGTP is up-regulated [2]. MT and SGTP are involved in the resistance mechanism in acute leukaemias [6]. There are several reports that dysfunction of SGTP and impaired function of the mechanisms of detoxification of environmental or endogenous carcinogens may increase susceptibility to myelodysplastic syndromes [8]. Enhanced expression of MT in cells induces an antiapoptotic effect. [9].

CML and OMF are myeloproliferative disorders resistant to standard chemotherapy. Treatment of MPD is mainly directed towards palliation. The only curative option for younger patients with CML and OMF is allogeneic bone marrow transplantation. We demonstrate increased SGTP and MT expression in the bone marrow of MPD patients. There is evidence that levels of MT are increased in proliferating cells and differing fibroblasts [9]. Of the myeloproliferative disorders in OMF extremely pronounced bone marrow stromal fibroblast proliferation is observed. In our study levels of MT in OMF patients were higher than in those with CML. This suggests that MT expression may correlate with bone marrow fibrosis. These data, although based on a relatively small number of patients, raise the possibility that SGTP and MT may play a role in the pathogenesis of MPD. The clinical significance of this phenomenon needs further investigation.

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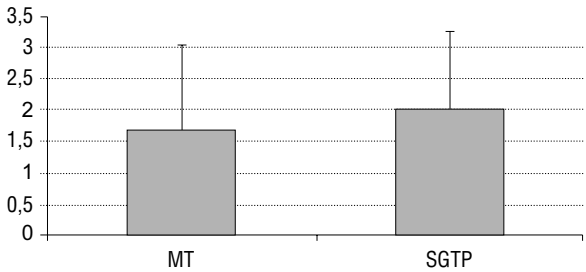

Figure 1. Expression MT and SGTP in MF.

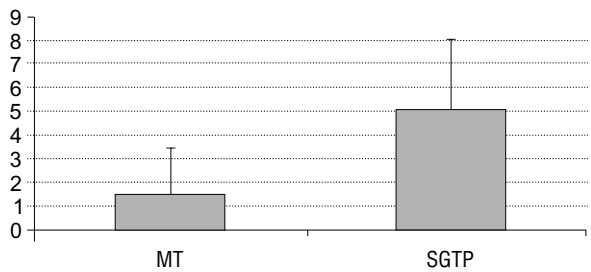

Figure 2. Expression MT and SGTP in CML.

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