Abstract

Glycogen synthase kinase-3 beta (GSK-3β) is a serine/threonine kinase involved in glycogen metabolism, in cell cycle progression, differentiation and embryogenesis.

One of the major biological functions of GSK-3β is to inhibit β-catenin by sequestration and promotion of its proteasomal degradation in the Wnt canonical pathway. Aberrant GSK-3β has been implicated in the pathogenesis of many disorders such as diabetes, Alzheimer's and Parkinson's disease and cancer. The biological role of GSK-3β in classical Hodgkin lymphoma (cHL) has not yet been clarified.

Three tissue microarrays (TMA) for immunohistochemical studies were obtained from formalin-fixed paraffin-embedded samples collected at diagnosis from 100 cHL patients. TMA sections were investigated by antibodies reactive with total GSK-3β, pY216 and pS9 GSK-3β and β-catenin. Three samples of hyperplastic lymph nodes were added. The mRNA expression profile of GSK-3β in normal B-cells populations, plasma cells (PC) and cHL microdissected neoplastic cells was performed.

We observed that GSK-3β was present in 100% of cHL cases with a range of positivity from 10% to 100% and a mean expression of 65% of positive Hodgkin and Reed Sternberg cells. The germinal centres of the reactive follicles showed a diffuse cytoplasmic positivity of the kinase in both centrocytes and centroblasts (CB). The mRNA expression levels were significantly higher only in CB compared to the neoplastic population ($P = 0.0004$). Positive stimulatory pY216 GSK-3β has been observed in 100% of cHL cases with a range of positivity in the neoplastic population from 8% to 100% and a mean expression of 56% of positive malignant cells. The active form of the kinase was predominantly relocated in the nucleus of the Hodgkin and Reed-Sternberg cells. Among the 100 samples, 20 were assessed positive for the inhibitory pS9 GSK-3β with a range of positivity in the neoplastic population from 1% to 58% and a mean expression of 8%. β-catenin was detected only in 12% of the cases with a predominant localization in the nucleus. Interestingly, a statistically significant association between the β-catenin positivity and the inhibitory pGSK-3β expression was observed ($P = 0.013$).

We report a different modulation of GSK-3β gene transcription supported by a constitutive activation of the kinase in cHL, resulting in the negative regulation of β-catenin and an altered physiological turnover of the kinase. These data suggest GSK-3β as a promising novel target for therapeutic intervention in cHL.