

Immunity to SOX group B and ZIC2 antigens: novel neuro-ectodermal targets and clinical indicators in small cell lung cancer

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Lung cancer is the most lethal tumor type in the US and Europe, with small cell lung cancer (SCLC) accounting for 15 to 18% of these cases (1, 2). SCLC is one of the most aggressive of all cancers, with up to 70% of patients presenting with distant metastasis at time of diagnosis (3, 4). Despite being initially responsive to therapy, currently the average survival for SCLC cases with limited disease is about 18 months, while patients with extensive disease survive about 9 months from the date of diagnosis (5). New treatment modalities are therefore urgently needed.

The search for antigenic targets that could be utilized as part of a vaccine therapy in cancer has been an area of intense research. Identifying the array of antigenic targets in SCLC and understanding whether such responses can result in anti-tumor immunity is critical, and may lead to successful immune vaccination against SCLC. We identified SOX Group B and ZIC2 proteins as highly immunogenic neuro-ectodermal antigens in SCLC by SEREX (6). We recently completed the analysis of 90 SCLC patients, 42 (47%) of whom had antibodies to either SOX1 or ZIC2. None had autoimmune paraneoplastic disease. SOX1, 2 and 3 antibodies were present in 28, 22 and 16% of patients respectively and 28% had ZIC2 antibodies. All patients with SOX2 and/or SOX3 antibodies were SOX1 seropositive. In contrast, only 8 patients (9%) had both SOX and ZIC2 antibodies. 36% of SOX1 seropositive patients had titers equal to or greater than 1:10⁶. Antibody titers against all antigens were highest at time of diagnosis and stable up to 6 months after. Seroreactivity against either SOX1 or ZIC2 showed statistically significant correlations with younger age, female gender, lower LDH levels and better response to initial therapy. Trends towards better overall survival, a larger proportion of limited stage disease and longer times to progression were observed for all seropositive patients when compared to seronegatives.

A significant number of neuro-ectodermal antigenic proteins were independently isolated as immune targets in autoimmune paraneoplastic neurological disease (PND) associated with SCLC (7). Despite the infrequent occurrence of autoimmune PND, antibodies to neuro-ectodermal antigens associated with PND, such as Hu or VGCC occur in up to 25% of SCLC patients (8, 9, 10, 11). The presence of anti-neuro-ectodermal antigens in SCLC has been associated with clinical parameters of less aggressive disease (9, 12). Thus, immune responses directed against multiple neuro-endocrine tumor antigens might relate to a better prognosis in SCLC (13).

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