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Development of SCLC immunotherapy using isoaspartylated ELAVL4

Laird-Offringa
Keck School of Medicine of USC, USA

Small cell lung cancer (SCLC) patients can develop autoimmune responses against neuronal proteins misexpressed in their tumors. Rarely, this response is severe, resulting in debilitating disease and death. One family of antigens is the neuronal embryonic lethal altered visual system-like (ELAVL) RNA-binding proteins ("Hu" proteins). All SCLC tumors misexpress neuronal ELAVL proteins, most commonly ELAVL4. Although less than 1% of SCLC patients develop high titer anti-ELAVL antibodies and exhibit paraneoplastic encephalomyelitis/sensory neuropathy (PEM/SN), lower titer antibodies are seen in about 15-20% of SCLC patients without autoimmune symptoms. Based on the sequence and presumably unstructured nature of the N-terminal region of neuronal ELAVL proteins, we hypothesized that in the context of SCLC these proteins can undergo isoaspartylation, an immunogenic post-translational modification, triggering an immune response in a subset of SCLC patients. Indeed, we recently showed that neuronal ELAVL proteins undergo isoaspartylation *in vitro* and *in vivo*, that this makes these proteins highly immunogenic and that sera from SCLC patients react specifically with the isoaspartyl-prone N-terminal region of ELAVL4. Here, we build upon these results by using a SCLC mouse model to develop and test a variety of immunization methods to determine whether mice can be protected from induced SCLC, laying the foundation for immunotherapy.

e: ilaird@usc.edu