Somatic mutations in CD8+ cells in multiple sclerosis patients and controls

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Background: Somatic mutations have a central role in cancer but their role in other diseases such as autoimmune disorders remains unclear. Indirect evidence for somatic mutations in multiple sclerosis (MS) patients' autoreactive T-lymphocytes was shown in 1990s using an HPRT reporter assay. In a recent pilot study, using next-generation sequencing, we have demonstrated directly that >50% MS patients harbor persistent small clones with somatic mutations, particularly in CD8+ cells.

Aims: To analyze the frequency of somatic mutations and possible mutational hot-spots in CD8+ cells in MS patients and age- and sex-matched controls.

Methods: 21 newly-diagnosed relapsing MS patients' (mean age 35.0, range 23-55, 76% females) and 21 controls' (mean age 35.2, range 23-57, 76% females) peripheral blood was fractionated into CD4+, CD8+, CD19+ cells. We performed deep next-generation sequencing of the CD8+ cells' DNA and control DNA targeting to coding regions of 2555 immune and cancer-related genes to detect somatic mutations.

Results: We discovered nonsynonymous somatic mutations in all MS patients and controls in the CD8+ fraction. The median number of mutations (n=4), and median allelic fraction (0.5%) were similar in the MS and control group. The number of mutated genes/mutations was 133/215 in patients and 150/251 in controls, 32% of the mutations were predictably deleterious in both groups. There were no obvious mutation hotspots, although a known activating STAT3*D661Y mutation, discovered in our pilot study, was detected in a second MS patient resulting in a frequency of 5.4% (2 out of 37 patients tested).

Conclusions: We have outlined an efficient approach for screening somatic mutations in blood. These results define a rather individual landscape of **s**omatic mutations in CD8+ cells in both MS patients and controls. The role of the mutant CD8+ clones in MS is unclear, but their potential role as drivers of chronic autoimmunity warrants further research.