The mitochondrial DNA constitution shaping T cell immunity in patients with rectal cancer at high risk of metastatic progression

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Abstract

A significant percentage of colorectal cancer patients proceeds to metastatic disease. We hypothesised that mitochondrial DNA (mtDNA) polymorphisms, generated by the high mtDNA mutation rate of energy-demanding clonal immune cell expansions and assessable in peripheral blood, reflect how efficiently systemic immunity impedes metastasis. We studied 44 rectal cancer patients from a population-based prospective biomarker study, given curative-intent neoadjuvant radiation and radical surgery for high-risk tumour stage and followed for metastatic failure. Blood specimens were sampled at the time of diagnosis and analysed for the full-length mtDNA sequence, composition of immune cell subpopulations and damaged serum mtDNA. A high mtDNA variant number, coexisting with an mtDNA non-H haplogroup, was associated with low risk of a metastatic event. Abundant mtDNA variants correlated with proliferating helper T cells and cytotoxic effector T cells in the circulation. Patients without metastatic progression had high relative levels of circulating tumour-targeting effector and natural killer T cells and, of note, the naïve (LAG-3+) helper T cell population, all inversely correlated with cell-free damaged mtDNA in serum known to cause antagonising inflammation. The statistical associations suggested that patient's constitutional mtDNA manifests the helper T cell capacity to mount immunity that controls metastatic susceptibility.

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