Regulation of the germinal center reaction and somatic hypermutation dynamics by homologous recombination.

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Abstract

During somatic hypermutation of immunoglobulin (Ig) genes in germinal center B cells, lesions introduced by activation-induced cytidine deaminase (AID) are processed by multiple error-prone repair pathways. While error-free repair by homologous recombination (HR) is crucial to prevent excessive DNA strand breakage at AID off-target genes, its role at the hypermutating Ig locus in the germinal center is unexplored. Using B cell-specific inactivation of the critical HR factor *Brca2*, we detect decreased proliferation, survival and thereby class switching of *ex vivo* activated B cells. Intriguingly, an HR defect allowed for a germinal center reaction and affinity maturation *in vivo*, albeit at reduced amounts. Analysis of somatic hypermutation revealed that a certain fraction of DNA lesions at C:G base pairs was indeed repaired in an error-free manner via Brca2 instead of being processed by error-prone translesion polymerases. By applying a novel pseudo-time *in silico* analysis of mutational processes, we found that the activity of A:T mutagenesis during SHM increased over time in Ctrl but not in *Brca2*-deficient mice. These mutation pattern changes in *Brca2*-deficient B cells were mostly specific for the Ig V region, suggesting a local or time-

dependent need for recombination repair to survive high rates of somatic hypermutation and especially A:T mutagenesis.

Beteiligte Forschungseinheiten

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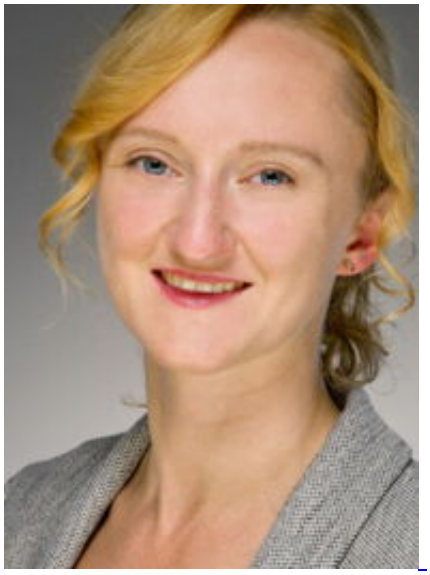
Details



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