Role of RNA in Targeting AID to DNA in B Cell Immunity and Cancer

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Abstract: DNA double strand breaks (DSBs) constitute one of the most toxic lesions to occur in a cell. Unrepaired DSBs can either lead to cell death or can participate in chromosomal translocations that are hallmarks of many kinds of tumors, including lymphomas. Thus, all living organisms, from bacteria to humans, have evolved robust pathways to rapidly and efficiently repair DSBs that are inadvertently generated during replication or through exposure to genotoxic stress such as ionizing radiation. Yet, despite the toxicity associated with DSBs, during the immunoglobulin (Ig) gene diversification process of class switch recombination (CSR), DSBs are deliberately introduced into defined regions, called switch (S) regions, of the B cell genome, and a failure to introduce such DSBs lead to severe combined immunodeficiency syndromes. The DNA deaminase AID (activation induced cytidine deaminase) is essential for the generation of DSBs. While S regions (and the Ig gene associated variable region gene segments) are primary targets, AID has the potential to induce DSBs at non-Ig genes, including oncogenes. Such off-target DSBs are the major lesions behind the ontogeny of a large number of mature B cell lymphomas. We have now shown that non-coding RNA emanating from the S regions act as molecular guides to recruit AID to S regions. This proposal tests the hypothesis that switch transcripts not only recruit AID to S regions to facilitate CSR but also sequester AID from other genomic regions to prevent collateral damage during B cell gene diversification reactions.