

## The ataxia telangiectasia mutated kinase coordinates $\nu\kappa$ -to- $J\kappa$ recombination between alleles to enforce $Ig\kappa$ allelic exclusion

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Antigen receptor allelic exclusion is achieved through incompletely defined mechanisms that promote asynchronous initiation and subsequent feedback inhibition of V-to-(D) J recombination between antigen receptor loci on homologous chromosomes. The original feedback inhibition model speculated that  $Ig\kappa$  recombination events on one allele might activate signals that transiently suppress additional rearrangements on the other allele. DNA cleavage activates the DNA-dependent protein kinase (DNA-PK) near DNA breaks and the Ataxia Telangiectasia mutated (ATM) kinase throughout the nucleus. ATM phosphorylation of histone H2AX along broken DNA strands creates high-density binding sites for MDC1, which functions with H2AX to amplify some ATM signals by retaining ATM kinases in chromatin at DSBs. We have found in primary mouse pre-B cells that inactivation of ATM, but not DNA-PK, H2AX, or MDC1, leads to increased cleavage of  $Ig\kappa$  alleles and 3' $J\kappa$  segments independent of defects in coding join formation. This inhibition of  $Ig\kappa$  recombination correlates with ATM-dependent repression of Rag1 mRNA levels. We have shown that inactivation of ATM, but neither H2AX nor MDC1, causes a higher frequency of B cells exhibiting  $Ig\kappa$  allelic inclusion. Collectively, our findings suggest that the soluble pool of ATM kinases activated by  $Ig\kappa$  cleavage transduces signals that suppress the initiation of additional  $\nu\kappa$ -to- $J\kappa$  recombination events, and thereby helps enforce  $Ig\kappa$  allelic exclusion.

### Biography

Craig Bassing earned his Ph.D. from the Duke University School of Medicine under the mentorship of Dr. Xiao-Fan Wang. Bassing then trained as a post-doctoral fellow at Harvard Medical School under the tutelage of Dr. Frederick W. Alt. In 2005, Bassing established his own research lab at the Children's Hospital of Philadelphia Research Institute and the Perelman School of Medicine at the University of Pennsylvania. Bassing is an Associate Professor in the Department of Pathology and Laboratory Medicine, an Investigator of the Childhood Cancer Center, and an Associate Member of the Abramson Family Cancer Research Institute.

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