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The ataxia telangiectasia mutated kinase coordinates Vκ-to-Jκ recombination between alleles to enforce Igκ 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 Igκ 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 Igκ alleles and 3'Jκ segments independent of defects in coding join formation. This inhibition of Igκ 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 Igκ allelic inclusion. Collectively, our findings suggest that the soluble pool of ATM kinases activated by Igκ cleavage transduces signals that suppress the initiation of additional Vκ-to-Jκ recombination events, and thereby helps enforce Igκ allelic exclusion.

Biography

Craig Bassing earned his Ph.D. from the Duke University School of Medicine under the mentorship of Dr. Xiao-Fan Wang. Dr. Bassing then trained as a post-doctoral fellow at Harvard Medical School under the tutelage of Dr. Frederick W. Alt. In 2005, Dr. 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. Dr. 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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Diagnosis of lung adenocarcinoma by immunohistochemistry

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Introduction: Number of lung adenocarcinoma (ADC) patients increased in the past few decades. Treatment of non-small cell lung carcinoma depends of its histological type in era of target molecular therapy particulary of ADC.Thyreoid-Transcriptive-Factor-1(TTF-1), Napsin-A, Surfactant B and Cytokeratin7 (CK7) are highly specific in diagnosis of lung ADC. Aim:To evaluate optimal panel of monoclonal antibodies in diagnosis of lung ADC on small-sized biopsy lung samples.

Method: Analysis of 50 small-sized biopsy lung samples obtained by bronchoscopy and transthoracic needle lung biopsy. Diagnosis of ADC was established on hematoxillyn-eosin stained(H&E) samples and confirmed immunohistochemicaly by TTF-1, Napsin-A, Surfactant B and CK7.Descriptive statistical method (%) was used.

Results: TTF-1 specificity was 86%(43/50), Napsin-A- 82%(41/50), SurfactantB – 56%(28/50) and Cytokeratin7- 90%(45/50) in ADCs. Two monoclonal antibodies were positive in 24%(12/50)ADCs, one of them was necessiraly TTF-1 or Napsin-A. Three monoclonal antibodies were positive in 40%(20/50) and 4 in 36%(18/50) ADCs, respectively. There is (no) statistical significans in number of monoclonal antibodies for diagnosis of ADC.

Conclusion: No one monoclonalantibody is specific for one histological type of carcinoma and its origin. TTF-1, Napsin-A, SurfactantB and Cytokeratin 7 belong in optimal panel for diagnosis of lung adenocarcinoma.

Biography

Jelena Stojsic is a pathologist, Head of Department of Thoracopulmonary Pathology, Service of Pathology, University Clinical Center of Serbia, Belgrade, Serbia. She is interested particularly in the field of thoracopulmonary pathology, especially oncology. She has published more than 25 papers in referral, per-reviewedinternational medical journals. She is in the process for application her PhD thesis.

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