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Genetic basis of inherited bone marrow failure syndromes

Inherited bone marrow failure syndromes (IBMFSs) are rare disorders with underproductive bone marrow, varying degrees of low blood counts, physical malformations and risk of myelodysplastic syndromes, leukemia and solid tumors. Over 25 different syndromes have been characterized. Phenotypic overlap among the IBMFSs frequently limits the ability to establish a diagnosis based solely on clinical features. Over 80 IBMFS genes have been identified that functions in fundamental biochemical pathways such as DNA repair, ribosome biogenesis, telomere maintenance and cell survival. The large number of syndromes and associated genes and phenotypic overlap often renders genetic testing prolonged and costly. Correct diagnosis, treatment, and cancer surveillance often depend on identifying the mutated gene. In this presentation, data about the phenotypic complexity of the IBMFSs and leukemia risk will be described. The results of applying new genomic methods to facilitate diagnosis will be discussed. Lastly, genes that were recently discovered as associated with IBMFS will also be discussed.

Speaker Biography

Dr. Yigal Dror is the Head of the Haematology Section and Director of the Marrow Failure and Myelodysplasia Program, senior scientist at the Genetics and Genome Biology Program at The Hospital for Sick Children, Toronto, and a member of the Institute of Medical Sciences at the University of Toronto. Dr. Dror graduated from the Hadassah Medical School of the Hebrew University in Jerusalem, and completed pediatric residency in Kaplan Hospital, Rehovot, Israel. He completed clinical fellowship in pediatric hematology/oncology and a post-doctoral research fellowship in the field of hematopoiesis and marrow failure syndromes/ myelodysplasia at SickKids hospital, Toronto. In 2000 Dr. Dror assumed his current position as a clinician scientist at SickKids.His main clinical interests are in the area of bone marrow failure and myelodysplastic syndrome. His research focuses on characterization of stem cells and blood cells in these conditions, genetic etiologies and clinical outcome. He heads the Canadian Inherited Marrow Failure Registry. Dr. Dror's lab showed that Shwachman-Diamond syndrome (SDS) marrow progenitors are reduced, overexpress Fas and undergo apoptosis through the FAS pathway. SBDS-deficiency results in abnormal accumulation of functional FAS at the plasma membrane level. The slow cell growth of SDS cells is associated with increased levels of reactive oxygen species, and can be reversed by antioxidants. His lab also studied the landscape of mutations and affected genes in inherited bone marrow failure syndromes using samples and data from the Canadian Inherited Marrow Failure Regsitry. The lab identified PARN as a new IBMFS gene and described defects in ribosomes and telomeres that unravel previously unknown functions of PARN, and suggest a new disease mechanism in which PARN-deficiency disrupts the polyadenylated state of H/ACA box RNA molecules that in turn influences ribosome profile and telomere length. The lab also identified DNAJC21 as the second gene associated with SDS. His lab showed that IBMFS are associated with high risk (37%) of clones/MDS/AML in childhood, and found that SDS marrows are characterized by stromal dysfunction, increased angiogenesis and abnormal leukemia-gene expression in marrow progenitor cells

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