Hot Papers in Pediatric Hematology/Oncology

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An international team of researchers performed whole genome sequencing and other molecular biology techniques to identify a de novo mutation in one allele of the homologous recombination DNA repair gene, RAD51 in an adult with Fanconi Anemia (FA)-like disease whose parents and sibling are unaffected and not mutation carriers. As a child, the individual presented with growth delay, microcephaly, hydrocephalus, thumb and radius abnormalities, imperforate anus and improperly formed left testicle. Tests on patient-derived cells for diepoxybutane (DEB) and mitomycin C (MMC) were positive. Western blot analysis of lymphoblast and fibroblasts demonstrated a normal level of FANCD2 monoubiquitination consistent with a defect in the downstream branch of the FA/BRCA pathway. As a 23 year old adult, the individual has not developed marrow failure typically seen in FA patients not affected by rare biallelic mutations in BRCA1, BRCA2 or RAD51C. The individual thus far has not developed cancer.

This finding has implications for genetic counseling for families with a high risk of FA who had been typically screened for 1 of 17 mutated genes with autosomal recessive or X-linked inheritance. Understanding this de novo mutation may also help explain how the RAD51 gene protects DNA, how this mutation leads to malignancy, and how neurodevelopment is impacted by mutations in proteins of the downstream branch of this DNA repair pathway.


Investigators from the University of Cambridge developed a pipeline or algorithm to measure serum and cerebrospinal fluid (CSF) microRNAs from the miR–371–373 and miR–302/367 clusters which are overexpressed in all malignant germ cell tumors (GCTs), to distinguish pediatric patients with gonadal and extragonadal malignant GCTs from benign GCT, non-GCT tumor and non-tumor control groups. They used exogenous non-human spike-in cel-miR-39-3p and endogenous housekeeper miR-30b-5p for serum and CSF qRT-PCR quantification respectively, in a total of 45 specimens from 25 children (8 with malignant GCT, 12 with benign GCT and non-GCT tumors, 5 controls). A four-serum miRNA panel (miR–371a–3p, miR–372–3p, miR–373–3p and miR–367–3p): (i) showed high sensitivity/specificity for diagnosing pediatric extracranial malignant GCT; (ii) allowed early detection of relapse of a testicular mixed malignant GCT; and (iii) distinguished intracranial malignant GCT from intracranial non-GCT tumors at diagnosis.

These findings are important for several reasons. Since elevated alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) for diagnosis and follow-up are limited to certain
malignant GCT subtypes, (predominantly yolk sac tumor and choriocarcinoma, respectively) or may be elevated in non-malignant conditions, the initial management of primary gonadal GCTs is complete resection where possible regardless of serum AFP/HCG levels. For extragonadal disease (e.g., the retroperitoneum, mediastinum, intracranial), typical radiological findings and raised AFP/HCG markers alone may be sufficient for diagnosis. For AFP/HCG negative extragonadal cases, biopsy is required to establish diagnosis which has risks of morbidity, due to the difficulties in surgical access to these anatomical sites. Furthermore, disease-monitoring after malignant GCT diagnosis to detect early non-symptomatic relapse currently relies heavily on serial radiological imaging, with associated cumulative radiation exposure and second malignant neoplasm risk. Consequently, microRNAs which are short, non-protein coding RNAs that are highly stable in body fluid, may offer greater sensitivity/specificity as biomarkers for diagnosing and/or monitoring malignant GCTs when employed using appropriate quantification systems.


In a correspondence to the editor of *Nature Genetics*, scientists from St. Jude Children’s Research Hospital describe ‘ProteinPaint’, a web application for simultaneously visualizing genetic lesions (including sequence mutations and gene fusions) and RNA expression in pediatric cancers. The pediatric data set consists of 27,188 validated somatic coding lesions acquired at diagnosis or relapse from 17 subtypes of pediatric cancer, 252 pathogenic or loss-of-function germline lesions detected in >1,000 pediatric patients with 21 cancer subtypes and RNA sequencing data for 928 pediatric tumors from 36 subtypes. The data were compiled from five major studies (including the research referenced below) and will be expanded with the publication of additional pediatric cancer studies. The authors provide supplementary notes and figures to explain how to access and use genomic information in collaboration with adult cancer genome data portal, Catalogue of Somatic Mutations in Cancer (COSMIC) and various analyzing tools to help develop individualized cancer therapies.  

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The incidence of pediatric thromboembolism has steadily increased in the past decade. Although our adult counterparts have been quick to incorporate new oral anticoagulants into daily therapeutic practice, pediatric hematology has been more cautious to adopt these medications given the low number of clinical trials and the lack of a specific reversal antidote. We share the same excitement to find an alternative to the pain and trauma of subcutaneous injections, the dietary restrictions and frequent lab monitoring, but hesitate to increase use of these agents without a commercially available reversal agent. Siegal et al. recently published their findings on Andexanet alfa; a promising new agent designed to neutralize the anticoagulant effects of factor Xa inhibitors.
Andexanet is a recombinant human factor Xa decoy protein that binds and sequesters factor Xa inhibitors in the vascular space. The authors designed a two-part randomized control trial (ANNEXA-A and ANNEXA-R) to study the impact of two different administrations of Andexanet versus placebo in patients taking commercially available factor Xa inhibitors. The study population consisted of 101 healthy adult volunteers who were randomized and blinded to the study intervention. Statistically significant improvements were demonstrated in reduction of anti-factor Xa activity, reduction of unbound factor Xa inhibitor concentrations, and almost fully restored thrombin generation. Andexanet demonstrated these changes within 2-5 minutes, was reproducible and did not demonstrate serious adverse or thrombotic events. Their dramatic results provide optimism that an antidote for a new generation of factor Xa inhibitors is now within reach.


Although systemic mastocytosis is a rare diagnosis in children, the academic pediatric hematologist may be asked to evaluate patients for this disorder not infrequently. Referrals often come from pediatric immunologists and dermatologists interested to determine if peripheral evidence of abnormal mastocyte activity is a result of abnormal marrow proliferation. Carter et al. recently published a thorough review to guide the pediatric hematologist through patient assessment, diagnosis and management of pediatric mastocytosis. In particular, the authors focus on the interpretation of serum tryptase levels and bone marrow pathology to guide management. Records from 105 children who presented to the NIH with pediatric mastocytosis were reviewed in their publication. They found that organomegally was a strong indicator of systemic disease, that serum tryptase levels correlated with severity of disease and could be utilize to monitor disease resolution. With a better understanding of the pathophysiology of disease and improved markers to diagnose and monitor disease, we can better standardize our approach to the evaluation of this disorder.


In a recent issue of *Blood*, a collection of clinical review articles was published to provide comprehensive updates on some of the most poignant issues the sickle cell field is facing today. Topics reviewed include hydroxyurea and drug development, pulmonary hypertension, the role of neutrophils, platelets and inflammatory pathways, CNS complications, and gene therapy. Hogen et al. focused their comprehensive review on the progress made towards gene therapy for sickle cell disease. They review landmark discoveries that contribute to the process of safe and efficient gene transfer and high-level, stable gene-expression. Some of these discoveries include the characterization of the β-globin locus control region, the transition to lentiviral vectors, and the addition of alternate globin gene expression. There are currently three gene therapy trials open to the sickle cell population. The progress these authors outline not only presents optimism for this modality of curative therapy in sickle cell disease, but optimism for a treatment modal with potential applications to patients with other hemoglobinopathies.
Relapsed and refractory autoimmune cytopenias remain a frustrating disorder to manage for both the patient and physician. Common therapeutic interventions, including steroids and IVIG, risk acute and chronic toxicity for often only transient improvement in blood counts. Bride et al. carried out a prospective, multicenter clinical trial utilizing the mTOR inhibitor sirolimus (rapamycin) to treat 30 patients with autoimmune multilineage cytopenias. They report that the majority of children obtained a complete and sustained remission with very few side effects. In particular, the authors highlight a profound positive response in a cohort of 12 patients diagnosed with autoimmune lymphoproliferative syndrome (ALPS) and recommend sirolimus as an early therapeutic option. Additionally, their results suggest the pediatric hematologist consider the use of sirolimus for relapse/refractory autoimmune cytopenias secondary to Evans syndrome, common variable immunodeficiency, and systemic lupus erythematosus. Evidence towards a well-tolerated, safe and efficacious oral option for autoimmune cytopenias provides a hopeful alternative for a large range of children that suffer from this often chronic condition.