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Multiomic analysis of KMT2A-r pediatric acute myeloid leukemia

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OBJECTIVES/GOALS: Acute myeloid leukemia (AML) is the second most common leukemia among pediatric populations. Approximately 15% of pediatric AML cases have KMT2A gene rearrangements (KMT2A-r), which confers a worse prognosis. Our goal is to better characterize the biologic landscape of KMT2A-r pediatric AML. METHODS/STUDY POPULATION: This study utilizes deidentified peripheral blood and/or bone marrow samples banked in the Children's Mercy Tumor Bank Biorepository. We investigated four KMT2A-r pediatric AML patients and six patients with other AML subtypes using samples collected at diagnosis and remission that were stored in the "tumor bank." In addition, we assessed 47 tumor bank samples from patients with other leukemia subtypes. We performed differential expression (DE) analysis on bulk RNA sequencing comparing KMT2A-r and all other AML subtypes, as well as single-cell RNA sequencing and proteomic analysis on the larger cohort. We then coalesced these data to better identify processes and pathways that are dysregulated in KMT2A-r AML, specifically aiming to find those that were contributing to leukemogenesis. RESULTS/ANTICIPATED RESULTS: Transcriptomic analysis showed that HOXA10 and MEIS1, two genes associated with immature myeloid populations and KMT2A-r leukemias, were more highly transcribed in AMLs than other leukemias. In addition, our DE analysis showed significantly higher transcription of ITGA7, a gene shown to correlate with poorer prognosis in AML, in our KMT2A-r samples when compared to other AML subtypes. FAM46C, a tumor suppressor gene contributing to mRNA stabilization, was less highly expressed in KMT2A-r AML when compared to other AML subtypes. Of note, low expression of FAM46C is associated with poorer survival and treatment response in multiple myeloma, and our findings suggest it may also be relevant to AML. Proteomic analysis is currently in process. DISCUSSION/SIGNIFICANCE OF IMPACT: Transcriptomic analysis identifies unique molecular features of pediatric KMT2A-r AML. We anticipate that our proteomic data will do the same and will also corroborate our RNA findings. Taken in combination, these results will provide a more complete picture of the specific mechanisms contributing to this aggressive leukemic subtype.

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Topology optimization for personalized intracranial aneurysm implant design

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OBJECTIVES/GOALS: To develop a personalized computational framework integrating computational fluid dynamics (CFD) and topology optimization for designing intracranial aneurysm implants. The primary objective is to reduce intra-aneurysmal blood flow velocity and enhance thrombus formation for improved treatment outcomes. METHODS/STUDY POPULATION: Patient-specific aneurysm geometries were extracted from pre-treatment rotational angiograms. A CFD-driven topology optimization framework was employed to design implants that reduce intra-aneurysmal flow velocity. The fluid dynamics were modeled using Navier–Stokes equations and the structural integrity of the implants was ensured by linear elasticity equations. The solid isotropic material with penalization (SIMP) method was applied to optimize the implant's porous architecture, balancing flow reduction with structural support. COMSOL Multiphysics software was used to implement the optimization. RESULTS/ANTICIPATED RESULTS: The optimized implants demonstrated significant reductions in intra-aneurysmal blood flow velocity and improved hemodynamic conditions. Flow velocity within the aneurysm was reduced by 77%, and the fluid energy dissipation ratio showed a 78.9% improvement compared to pretreatment conditions. The optimized porous structures were tailored to the aneurysm's specific geometry, providing personalized designs that improve flow stasis and thrombus formation. Further validation of the implants will be performed in vitro and in vivo to assess their effectiveness and biocompatibility. DISCUSSION/SIGNIFICANCE OF IMPACT: This personalized implant design framework could lead to better treatment outcomes by reducing aneurysm recurrence and complications compared to current devices. It provides a pathway for improved occlusion rates and patient-specific solutions for intracranial aneurysms.

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Charting the metabolic biogeography of the colorectum in cancer: Challenging the right-sided versus left-sided classification

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OBJECTIVES/GOALS: Colorectal cancer (CRC) is classified into right-sided, left-sided, and rectal cancer. Clinicopathological and molecular features vary along the colorectum, even within subsites, leading to inconsistencies in identifying relevant biomarkers. We created a CRC metabolome map to explore diagnostic and survival heterogeneity across subsites. METHODS/STUDY POPULATION: A total of 372 patient-matched tumor and normal tissue samples were collected from seven colorectal subsites: cecum (n = 63), ascending colon (n = 44), transverse colon (n = 32), descending colon (n = 28), sigmoid colon (n = 75), rectosigmoid colon (n = 38), and rectum (n = 92). Liquid chromatography–mass spectrometry was used to compare metabolite abundances. Cox proportional hazards regression assessed metabolite impact on survival, adjusted for clinical covariates. Parametric and nonparametric tests were applied to compare the metabolite abundances. An interactive, publicly accessible online platform was developed to allow researchers to explore and generate hypotheses from this data. RESULTS/ANTICIPATED RESULTS: Our study identified 39 and 70 significantly altered metabolites, including bile acids and lysophosphatidylcholines, across tumors and normal mucosa, showing metabolic heterogeneity between CRC subsites. We observed significant linear trends in metabolite gradients from the cecum to the rectum, and it was depended on the disease status. Comparison of tumors to patient-matched normal mucosa revealed metabolite changes exclusive to each subsite. Metabolite differences correlated with survival were unique to each subsite. Additionally, we developed an interactive,

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