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Inflammatory Web Catches Vessels

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To most kids, the phrase “new jeans” means a trip to the mall. But for children with polyarteritis nodosa (PAN), “new genes” might mean life-saving new therapies. Recently, two independent research teams linked pediatric PAN with inactivating mutations in the *CECR1* gene, which encodes adenosine deaminase–2 (ADA2).

PAN is a rare but devastating multisystem disorder that afflicts both adults and children and is characterized by necrosis of blood vessels (vasculitis) in the brain, kidneys, and skin and structural abnormalities in the arteries (vasculopathy). Together, this damage manifests as a range of complications, such as arterial aneurysms, cerebral infarcts, hypertension, intracerebral hemorrhages leading to recurrent strokes, and digital gangrene. Despite its high morbidity, little is known about the molecular pathogenesis of PAN.

In the new studies, patient populations consisted of 7-month-old to 10-year-old children from Israeli, German, and Turkish families who presented with strokes, intraventricular hemorrhages, digital necrosis, and skin rashes. The presence of aneurysms as well as small-vessel inflammation and necrosis on biopsy were consistent with PAN. The early-onset and familial nature of the disease suggested a hereditary link, prompting whole-exome sequencing to search for potential disease-causing genes. Out of all of the genetic variants identified, *CECR1*, which encodes the enzyme ADA2, emerged as a candidate gene with multiple missense mutations. The frequency of the *CECR1* mutant allele was extremely low in the general population, and unaffected parents were heterozygous carriers of these mutations, conferring a recessive inheritance.

ADA2 participates in purine metabolism and is a growth factor for immune cells and monocytes (macrophage precursors). Patients with *CECR1* mutations displayed lower amounts of the ADA2 protein and enzymatic activity in serum relative to controls—observations that were corroborated with structural analyses. Further mechanistic experiments showed that silencing of *CECR1* in monocytes forced their development into proinflammatory macrophages, and co-culture with endothelial cells disrupted endothelial integrity. Silencing of the *CECR* gene in zebrafish partially recapitulated clinical features (intracerebral hemorrhage and neutropenia). Thus, it is likely that loss of both the enzymatic and growth factor functions of ADA2 results in the accumulation of adenosine, a proinflammatory metabolite, and tilts the balance toward a proinflammatory immune system. These components may conspire to weave a profoundly inflammatory milieu that embroils vessels (vasculitis) and disrupts endothelial integrity, resulting in vasculopathy.

This important discovery implicates *CECR1* as a candidate gene in a small fraction of pediatric familial PAN patients and may explain both the vasculitis and vasculopathy components of PAN. However, the precise pathogenic mechanism needs further elucidation. Although hailed as a new molecular marker and potentially a therapeutic target, ADA2's role in more common types of PAN and other vasculitidies remains to be determined.

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