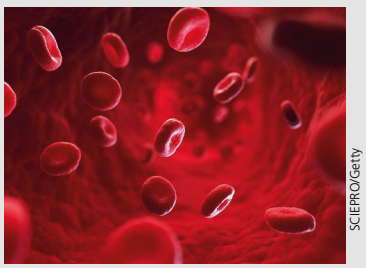
Genetics inMedicine | NEWS

NEWS

Key heart gene also regulates immune system



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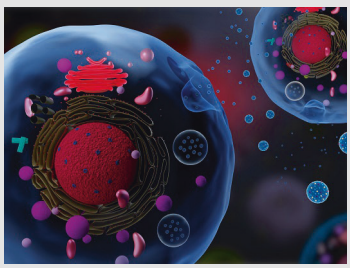
Variants in the cysteine-rich with EGF-like domains 1 (*CRELD1*) gene are associated with nonsyndromic atrioventricular septal defect, and mice lacking the gene die before birth, making *CRELD1* a critical player in embryonic heart development. In adulthood, *CRELD1* expression is ubiquitous, yet murine embryonic lethality poses challenges to determining the gene's function outside of heart development. As recently reported in *Nature Immunology* (https://doi.org/10.1038/s41590-020-00811-2), Bonaguro and colleagues make use of the extreme variance in *CRELD1* expression in large human cohorts to find that *CRELD1* modulates immune system homeostasis. The researchers examined whole-blood RNA-sequencing data in 95 individuals. By binning the top and bottom 10th percentiles, they generated a highly expressing *CRELD1* group (*CRELD1*^{HI}) and a lowly expressing *CRELD1* group (*CRELD1*^{LO}). When the researchers assessed immune-cell populations in blood between the groups, they found that *CRELD1*^{LO} donors had lower numbers of naive CD4$^+$ and CD8$^+$ T cells and more effector memory cells. The team then assessed the relationship between low CRELD1 expression and low numbers of naive CD4$^+$ T cells by generating viable conditional *CRELD1* knockout mice. Young mice lacking *CRELD1* were healthy, with T-cell numbers comparable to those in control mice. However, *CRELD1*-deficient mice older than 11 months had significantly lower T-cell numbers than controls. The researchers also saw markers of immunosenescence in the knockout mice, but not the controls. Together the results indicate that *CRELD1* knockout mice mirror the phenotypic features seen in *CRELD1*^{LO} individuals. RNA sequencing and gene set enrichment analysis of naive CD4$^+$ T cells further showed differences in T-cell homeostasis, activation, and apoptosis-associated programs between *CRELD1* knockout and control mice, as well as downregulation of Wnt signaling. When the researchers activated CD4$^+$ T cells by T-cell-receptor stimulation, naive CD4$^+$ T cells from knockout mice initially hyperproliferated but were subject to increased apoptosis, leading to reduced overall proliferation and T-cell loss compared with cells from control mice. The researchers then correlated the results back to humans. Differential gene expression analysis across 285 human CD4$^+$ T-cell transcriptomes revealed a similar enrichment signature between the *CRELD1*-deficient mice and low-*CRELD1*-expressing individuals, and principal component analysis between *CRELD1*^{LO} and *CRELD1*^{HI} individuals revealed clear phenotypic differences. The authors conclude that together the data indicate a role for *CRELD1* in regulating immune system homeostasis. —*V. L. Dengler, News Editor*

Variant in Cl^-/H^+ exchanger may underlie early-onset neurodegenerative disorder



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Neurons depend on the clearance of intracellular aggregates for normal function, a process that in turn is dependent on ion homeostasis and transport across endosomal and lysosomal membranes. The Cl^-/H^+ exchanger CLC6, encoded by *CLCN6*, functions mainly in late endosomes of the nervous system. In mice, lack of *CLCN6* leads to mild lysosomal storage disruption; however, the impact of *CLCN6* variants in human disease is not well established. In a recently published study in the *American Journal of Human Genetics* (https://doi.org/10.1016/j.ajhg.2020.11.004), Polovitskaya and colleagues report that a missense variant in *CLCN6* is associated with a severe, early-onset neurodegenerative disorder. The researchers identified a de novo change, c.1658A>G (p.Tyr553Cys), in *CLCN6* in three unrelated individuals with unclassified and extreme neurodegeneration. Partial sequence alignment revealed that the affected residue is highly conserved, while in silico predictive tools classified the variant as damaging/deleterious. All three individuals presented with developmental delay with early-onset regression, generalized hypotonia, and respiratory insufficiency requiring intervention. Magnetic resonance imaging additionally uncovered bilateral diffusion restriction in cerebral peduncles, dorsal brainstem, and/or dorsal midbrain. To determine the impact of the p.Tyr553Cys variant on ion transport, the researchers performed whole-cell patch-clamp analysis on Chinese hamster ovary cells transfected with wild-type or variant expression constructs. Currents in variant-transfected cells activated more slowly upon depolarization than wild-type transfected cells and reached higher steady-state amplitudes. In addition, currents in variant-transfected cells were insensitive to acidic extracellular pH, suggesting that transport activity would not decrease at the low pH of late endosomes, as in wild-type. When the researchers transfected wild-type CLC6 into HeLa cells, they saw that CLC6 localized to small cytoplasmic vesicles at late endosomes and lysosomes. However, CLC6-Tyr553Cys transfection resulted in obviously large vesicles (more than 2 μm). Live-cell imaging revealed that vesicle enlargement likely occurred via fusion events. In contrast, the team did not detect a difference in vesicle size or intracellular pH between control and patient-derived fibroblasts. The authors conclude that the *CLCN6* missense variant is associated with a severe clinical phenotype that allows clinical diagnosis. Overall, the work establishes *CLCN6* as a neurological disorder–associated gene. —*V. L. Dengler, News Editor*