Researchers reveal developmental mechanisms behind rare bone marrow disorder

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Myelodysplastic syndrome is an umbrella term used to describe disorders characterized by the bone marrow's inability to produce normal blood cells. Researchers from Charité - Universitätsmedizin Berlin have found that a mutation in a specific tumor suppressor gene is one possible reason why children with a very rare genetic disorder develop myelodysplastic syndrome. Results from this research have been published in the current edition of the *Journal of Clinical Investigation*.

The key symptoms of myelodysplastic syndrome (MDS) are a shortage of fully-functional red blood cells (erythrocytes), a shortage of certain white blood cells (leukocytes), and a shortage of platelets (thrombocytes). In a healthy person, these three types of cells are produced in the bone marrow. In patients with MDS, blood cell production is disrupted - a condition which may result in these patients progressing to acute myeloid leukemia (AML).

While looking for the cause of a rare disease, a team of researchers led by Prof. Dr. Annette Grüter-Kieslich, Head of the Department of Pediatric Endocrinology and Diabetology, discovered a potential trigger for MDS development in children with monosomy 7 of the bone marrow. All of these children had lost one copy of chromosome 7, whereas normally, a person has two copies of each of the 23 chromosomes found in the human body.

Working with colleagues in England and Freiburg, the researchers studied a total of seven children, all of whom presented with similar symptoms: congenital adrenal insufficiency, gonadal failure, and severe pulmonary infections. Using innovative genetic testing methods, the researchers identified mutations in a tumor suppressor gene, SAMD9, which is located on chromosome 7. Through additional testing in different cell systems, the researchers were able to show that these inherited mutations were responsible for the children's severe developmental problems. They were also able to show that both monosomy 7 and myelodysplastic syndrome developed in response to these mutations.

"Bone marrow cells which have lost the mutated chromosome 7 have a considerable selection advantage," explains Prof. Annette Grüters-Kieslich. She adds: "In patients with malignant conditions, complete or partial chromosome loss may not be a random event. Instead, it may represent a mechanism specifically aimed at eliminating genetic defects. The significance of this developmental mechanism for myelodysplasia, which has been described here for the first time, may therefore reach far beyond this rather rare disease."

The researchers are hoping to work with other centers in order to test whether SAMD9 mutations may also be responsible for causing other subtypes of myelodysplastic syndrome.

More information: Federica Buonocore et al, Somatic mutations and progressive monosomy modify SAMD9-related phenotypes in humans, *Journal of Clinical Investigation* (2017). DOI: 10.1172/JCI91913

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