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Polyubiquitinated protein depots in platelets and megakaryocytes from patients with ANKRD26-RT

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The Ubiquitin-proteasome system (UPS) is essential for protein metabolism in eukaryotic cells. Several neurodegenerative, cardiac and malignant/neoplastic diseases have been associated with altered or differential functional activity of the proteasome and the proteasome has been targeted therapeutically to treat patients with multiple myeloma (1). Although present in platelets (2), roles for the UPS in regulating platelet function are not obvious. It is also unclear how the UPS functions in inherited or acquired disease processes that affect megakaryopoiesis and/or thrombopoiesis.

In this issue of *Thrombosis and Haemostasis*, Necchi et al. (3) demonstrate increased formation of Particulate Cytoplasmic Structures (PaCSs) in megakaryocytes and platelets from patients with autosomal-dominant ANKRD26-related thrombocytopenia (ANKRD26-RT). PaCS are depots that resemble the barrel-like proteasome unit and show selective immunoreactivity for the proteasome and polyubiquitinated proteins. They were first observed by the same group in *H. pylori*-infected epithelium and then in a variety of epithelial neoplasms and neutrophils of the Schwachman-Diamond Syndrome. Until now, PaCS have not been identified in platelets or their precursors. Using a variety of techniques including electron microscopy and western blot analysis, Necchi et al. demonstrate increased number and size of PaCSs in platelets and stem-cell differentiated megakaryocytes from patients with ANKRD26-RT compared to healthy control subjects. Interestingly, this observation was distinct from other forms of inherited and immune thrombocytopenia and was restricted to cells of the megakaryocytic lineage which implies that the local accumulation of UPS components may contribute directly to the disease phenotype.

The pathogenesis of ANKRD26-RT is unknown and likewise, the precise role of PaCSs in platelets is not obvious. However, PaCSs were found in a subset of platelets isolated from healthy controls indicating that these structures may be involved in both physiologic and pathophysiologic functions of these anucleate cytoplasts. Future studies will undoubtedly

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Conflicts of Interest

None declared.

deliver more news regarding the role of the UPS and PaCSs in megakaryocyte and platelet biology.

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