Title: RNA binding proteins and localized RNA determining platelet function

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Abstract

Although the main function of platelets is in thrombosis, their role in many pathophysiological processes is emerging. Platelets are produced by megakaryocytes (MKs) via complex process including polyploidization, membrane system establishment and cytoplasmic expansion. Despite lacking a nucleus, platelets carry a diverse repertoire of functionally significant RNAs derived from their parent MK, which importance in MKs and platelet biogenesis has started unfolding. Frequent mutations in splicing factor genes in hematological malignancies demonstrate that blood lineages are particularly vulnerable to RNA processing defects. We recently showed that the splicing factor SRSF3 is essential for megakaryocyte maturation and generation of functional platelets. SRSF3 was found to control platelet biogenesis by binding to RNAs involved in megakaryocyte maturation and platelet production.

To enhance our understanding of the MK and platelet RNA biology, we have established cell models that enable the investigation of RNA processing mechanisms involved in MK and platelet biogenesis as well as the role of different RNAs in platelet function. Our megakaryoblast differentiation model faithfully mimics the *in vivo* maturation of MK culminating in platelet release. By using RNA proximity labelling, cellular fractionation, and high-resolution imaging, we can track how RNA binding proteins sort RNAs within the MK and into platelets. We aim to understand how RNA processing controls the MK maturation process, how specific RNAs are localized to the platelet release sites during MKs differentiation, how specific RNAs regulate platelet biosynthesis and function, and how platelet RNAs are involved in platelet-related diseases.