Functional analyses of cell polarity organization in human hematopoietic stem and progenitor cells

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Freshly isolated hematopoietic stem and progenitor cells (HSPCs) are small, round cells which adopt a polarized cell shape upon cultivation. Depending on the activity of the phosphoinositol-3-kinase (PI3K) they form a leading edge at the front and a uropod at the rear pole. We have recently shown that in addition to different lipid raft associated proteins, the lipid raft organizing molecules Flotillin-1 and -2 get highly concentrated at the tip of the uropod. Performing pharmaceutical inhibitor studies we dissected mechanisms controlling HSPC polarization and were able to discriminate two levels of cellular polarization. According to our observation the vast majority of freshly isolated human HSPCs, i.e. umbilical cord blood derived CD34⁺ cells, show a random distribution of the Flotillins and other lipid raft associated molecules like ICAM3. Upon cultivation they redistribute these molecules to form a crescent and thus become intrinsically polarized, before they adopt their characteristic morphological polarized cell shape. Using this discrimination, we obtained evidence that PI3K and atypical protein kinase C (aPKC) activities are required to organize the intrinsic polarity while the morphological polarization process also depends on protein synthesis, actin polymerization and rho-GTPases activities.

Since aPKCs form an evolutionary conserved complex with the partitioning defect proteins Par3 and Par6 as well as with the rho-GTPase Cdc42 and this complex has been found to organize cell polarity in many organisms and tissues, we decided to investigate the function of the individual components on the cell polarization process of human HSPCs next. Due to the fact that the Par/aPKC complex also coordinates asymmetric cell divisions in a number of systems and as we showed that human HSPCs can divide asymmetrically, we have started to study the impact of these proteins on the cell fate of human CD34⁺ cells in parallel. Our pharmaceutical studies as well as our experimental strategy within the Par/aPKC project together with some preliminary results will be presented.