NEW FRONTIERS IN NEUROACANTHOCYTOSIS AND NEURODEGENERATION WITH BRAIN IRON ACCUMULATION: FROM BENCHSIDE TO BEDSIDE

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Title

IN ChAc RED CELLS THE ABNORMALLY ACTIVATED LYN AFFECTS ANKYRIN MULTIPROTEIN COMPLEXES AND IS INHIBITED BY DASATINIB

Authors

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Chorea-acanthocytosis (ChAc) is a hereditary neurodegenerative disorder, one of the neuroachantocytosis syndromes (NA). One of the hallmarks of NA is the presence of circulating acanthocytes, generation of which is still under investigation. Recently, we reported increased Tyr-phosphorylation state of the red blood cell (RBC) membrane proteins from ChAc patients, related to abnormal activation of Lyn, an Src family kinase (SFKs) (Blood 118; 5652; 2011). In the context of international collaboration, we further characterized Lyn signaling pathway in RBC from ChAc patients. In ChAc RBCs, we found a weakness of ankyrin-based multiprotein complex bridging the membrane to the cytoskeleton, contributing to the generation of acanthocytes. We then evaluated the state of Lyn (active-inactive) in the cytoplasmic fraction from RBC of ChAc patients. In ChAc RBCs we found higher levels of Phospho- Lyn-396, corresponding to active Lyn, compared to controls. We then evaluated whether classical Lyn inhibitors such as PP2 or Dasatinib, a pharmacological Lyn inhibitor, might block Lyn in ChAc RBCs. We found that both PP2 (0.1μM) or Dasatinib (0.1 μM) were able to efficiently inhibit Lyn in both ChAc and healthy RBCs. These data suggest that in ChAc (i) the abnormal activation of Lyn affects RBC membrane mechanical stability weakening both multiprotein complexes, bridging the membrane to the cytoskeleton; (ii) Lyn activity is inhibited by either PP2 or Dasatinib, suggesting Lyn as possible new therapeutic target in ChAc.

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