学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
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Morphogenesis of ellipsoidal camelid red cells: a possible role of a hyperstable membrane skeleton due to a novel alternatively spliced 4.1R
（ラクダ科動物の赤血球が楕円形である仕組み：特徴的構造をもつ 4.1R による膜骨格の超安定化作用）

The red blood cells (RBCs) of vertebrates have evolved into two basic shapes, with nucleated nonmammalian RBCs having a biconvex ellipsoidal shape and anuclear mammalian RBCs having a biconcave disk shape. However, the evolutionary molecular mechanism responsible for the difference between ellipsoidal and discoidal shaped RBCs remains unclear. In contrast to other mammalian RBCs, camelid RBCs are flat ellipsoids with reduced membrane deformability, suggesting altered membrane skeletal organization. The characterization of membrane skeletons in camelid RBCs may therefore enable a determination of the mechanisms that underlie the evolutionary divergence of RBC shapes. The present study showed that protein 4.1R, a major component of the membrane skeleton, of alpaca RBCs contains an alternatively spliced exon 14-derived cassette (e14) not observed in the highly conserved 80 kDa 4.1R of other highly deformable biconcave mammalian RBCs. The inclusion of this exon, along with the preceding unordered proline- and glutamic acid-rich peptide (PE), results in a larger and unique 90 kDa camelid 4.1R. Human 4.1R containing e14 and PE, but not PE alone, showed markedly increased ability to form spectrin–actin–4.1R ternary complex in viscosity assays. A similar facilitated ternary complex was formed by human 4.1R possessing a duplication of the spectrin–actin-binding domain, one of the mutations known to cause human hereditary elliptocytosis. The e14- and PE-containing mutant also exhibited an increased binding affinity to β-spectrin compared with wild-type 4.1R. These findings indicate that the presence of 4.1R protein with the e14 cassette results in the formation and maintenance of a hyperstable membrane skeleton, resulting in rigid red ellipsoidal cells in camelid species, and suggest that membrane structure is evolutionarily regulated by alternative splicing of exons in the 4.1R gene.