Structural Insights into the Organization of Membrane Skeleton in Red Blood Cells

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Spectrin-based membrane skeleton is a ubiquitous structure of metazoan cells. In erythrocytes, this skeleton, as a membrane-associated polygonal network, confers exceptional strength and elasticity to the lipid membrane to tolerate the shear stress in circulation. Defects in membrane skeleton cause a variety of red blood cell disorders. Here, we report the cryo-EM structures of the native spectrin-actin junctional complex, which is a highly decorated short filamentous actin (F-actin) acting as a central organizational unit of the erythrocytic membrane skeleton. The structures reveal general principles underlying the organization and assembly of the skeleton and elucidate specific molecular roles for the components of the junctional complex. While a hetero-tetramer of α- and β-adducin binds to the barbed end of the junctional complex as a flexible cap, tropomodulin and a newly identified factor SH3BGRL2 together create an absolute cap at the pointed end. Three copies of dematin, present in the central actin layers, form parallel ring-like structures encircling the junctional complex. The structures also provide atomic details for the docking of tropomyosin on the junctional complex, including its interactions with the capping proteins and successive attachments with the trunk of the junctional complex. Overall, this work serves as a structural framework for understanding the assembly and dynamics of the membrane skeleton in erythrocytes, and also offers insights into mechanisms of related ubiquitous F-actin binding factors in other types of F-actin systems.