Department of Biosciences and Nutrition

Evolution and transcriptional regulation of Kindlins

Akademisk avhandling

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Abstract

Kindlins are relatively newly discovered focal adhesion proteins. The Kindlin family includes three highly conserved proteins: Kindlin-1, Kindlin-2 and Kindlin-3. All three Kindlins have been shown to interact with Integrin and this interaction plays important role in the functional properties of Kindlins. We here in explore for the first time the evolutionary history of these proteins. The phylogeny of the Kindlins suggests a single ancestral Kindlin protein present in the earliest metazoans e.g. sponges. This protein then underwent duplication events in insects and also experienced genome duplication in vertebrates, leading to the Kindlin family. A comparative study of the Kindlin paralogs showed that Kindlin-2 is the slowest evolving protein among the three family members and is evolving under strong purifying selection.

The FERM domain of each Kindlin is bipartite because of the unique insertion of PH domain, dividing the FERM domain into two domains. The FERM domain plays a key role in integrin activation. In one of our study, we tried to trace the evolutionary history of Kindlin FERM domain with respect to the FERM domain of other proteins. We showed that although Kindlin proteins have highly conserved domain among themselves, their FERM domain however is much less conserved when compared with the FERM domain containing proteins of B4.1 superfamily. In addition, we showed that the unique insertion of Pleckstrin homology (PH) like domain in Kindlin FERM domain have important evolutionary and hence functional consequences. We also traced the important residues in Kindlins by ranking them according to their evolutionary significance and discussed about the structure-function relationship of these ranks. We hypothesized that FERM domain originated from a proto-Talin protein in a unicellular or proto-multicellular organism and the advent of multicellularity was accompanied by a burst of FERM domain containing proteins (FDCPs) which supported the complex organization multicellularity requires.

Despite of having strong homology, Kindlins exhibit very contrasting expression profile where Kindlin-2 shows broad spectrum of expression while Kindlin-1 and Kindlin-3 are tissue specific and expressed predominantly in epithelial and hematopoietic system respectively. The expression pattern of Kindlins along with phylogenetic studies supports the subfunctionalization model of gene duplication. In one of our study, we tried to explore the evolutionary changes occurring in the regulatory regions of Kindlin genes. We found that, as with coding region, Kindlin-2 promoter is the most conserved promoter in Kindlin paralogs. We also showed that the conservation profile of Kindlin expression pattern in mammals very much go in line with the conservation of regulatory sequences. In addition, we made use of ENCODE histone modification data and showed that although a correlation is found between Kindlin expression pattern and extent of modification of H3K4me3, the conservation pattern of this epigenetic signature does not match much with the conservation of Kindlin expression. The *in silico* studies we performed on Kindlin promoters also provided us a platform to target the potential transcription binding sites and hence characterize these promoters functionally. In this direction, we studied the role of GLI1, SP1 and SRF in the transcriptional regulation of Kindlin-2.

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