LETTER

Fold class and evolutionary mobility of protein modules

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Reversion-inducing Cysteine-rich Protein with Kazal Motifs (RECK) protein contains five tandem extracellular CC domains that play an essential role in the regulation of signaling by WNT7A and WNT7B. As pointed out by Chang et al. (1), in the RECK gene the CC domains are encoded by exons flanked by phase 1 introns, a genomic feature known to facilitate the spread of class 1-1 modules through exon shuffling (2). However, in striking contrast to other similarly sized class 1-1 modules (epidermal growth factor, fibronectin type 3, thrombospondin type 1, etc.) that are present in a vast variety of multidomain proteins of metazoa, CC domains are present only in RECK proteins.

Although such a difference in the evolutionary mobility of class 1-1 modules is remarkable, we disagree with the conclusion of Chang et al. (1) that the lack of mobility of CC domains is an evolutionary anomaly. In our view it just highlights the fact that the frequency of joining a given domain type to other domains to create novel multidomain architectures is controlled both by the probability of such a genetic change and the probability of its fixation. The most mobile extracellular modules have acquired this status as a result of a combination of special genomic features of the genes and structural and functional features of the protein domains (3). It is generally accepted that the folding autonomy of modules of multidomain proteins is of utmost importance for their mobility as this minimizes the influence of neighboring domains (4). Folding autonomy can ensure that folding of the domain is not deranged when inserted into a novel protein environment. It thus seems very likely that the most widely used domains have been selected according to the rate, robustness, autonomy of folding, and stability of the domain.

We have pointed out earlier that modules used most frequently in the construction of extracellular modular proteins are not random representatives of the protein fold universe (5). Modules of the highest mobility belong to the mainly β class of proteins, with only a negligible fraction being assigned to the mainly alpha class of protein folds (5). It is noteworthy in this respect that the extracellular RECK CC domain belongs to the all-alpha class of protein folds: It has been found to fold into a compact four-helix bundle, stabilized by three disulfide bonds (1).

The lack of mobility of RECK CC domains is thus in harmony with our observation that all-alpha protein folds are underrepresented among mobile extracellular protein domains (5). It is not clear, however, why all-beta folds are favored, whereas all-alpha protein folds are counterselected among mobile extracellular modules. The fact that the structural distribution of disulphide-bonded extracellular domains is in general shifted toward the mainly β proteins (6) suggests that such proteins are more stable in the extracellular environment than other fold classes.

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