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No Sec7-homology domain in guanine-nucleotide-exchange factors that act on Ras and Rho

Abergel and co-workers[1] argue in a recent *TiBS* article that CDC25- and Dbl-homology (DH)-domain-containing proteins, such as mouse guanine-nucleotide-releasing protein (GNRP), also contain a Sec7-homology domain. They base this argument on limited sequence similarity that, apparently, cannot be detected by standard similarity-search programs but can be identified by a regular-expression search. The alignment that Abergel *et al.*[1] present includes an 18-residue insertion in the H α-helix, which, in the yeast Sec7 homologue Gea2p, is intimately involved in recognition of the ARF-like GTPase[2]. Consequently, the authors argue that that this region of mouse GNRP is likely to have assumed a function distinct from that of Sec7 and Gea2p, which are guanine-nucleotide-exchange factors (GEFs) that act on ARF-like GTPases.

This prediction surprised us considerably, because previous, standard similarity-search-program analyses indicated that the region of mouse GNRP (residues 520–713) that Abergel *et al.* propose is homologous to Sec7 in fact represents the C-terminal region of a pleckstrin homology (PH) domain[3] and the N-terminal portion of the REM domain (also known as the N domain) of SOS-like Ras GEFs[4–7] (Fig. 1). Annotation of the mouse GNRP PH domain in SWISS-PROT[8] and detection of both domains by using utilities such as Pfam[9], SMART[10] or Profilescan[11] might have alerted Abergel *et al.* to these previously published predictions.

A statistically significant relationship shared by members of the family of RasGEF REM domains, including the REM domain of mouse GNRP, can be established by standard methods. A PSI-BLAST[12] search with the N-terminal region of mouse RALGDS (GenBank identifier 544402; residues 1–317) and an *E*-value-inclusion threshold of 0.001 recovers the RasGEF REM domains shown in Fig. 1 of Ref. 1, as well as that of SOS (the structure of which is known[6]), within three iterations; the *E* values obtained are $<10^{-3}$ (for human and mouse RASGRF2, $E = 10^{-4}$ by iteration 2; for human CDC25, and rat and mouse GNRP, $E = 10^{-11}$ by iteration 3).

Within the past year, high-resolution structures of Sec7 homologues[2,13–15], and the REM and CDC25-like domains of SOS have been published[6]. These, taken together with the significant relationships between the REM domains, demonstrate that the folds of the two Sec7 subdomains do not resemble the folds of either the PH or the RasGEF REM domain.

In conclusion, standard similarity-search methods can make statistically significant predictions that CDC25-like, PH and RasGEF REM, but not Sec7, domains are present in GNRPs (multiple alignments of these domain families are available[9,10]). Clearly, improvements in

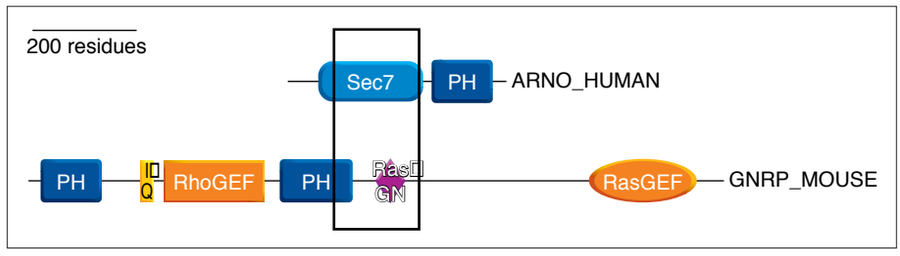

Figure 1
Domain organization of mouse guanine-nucleotide-releasing protein (GNRP) and the human Sec7 homologue ARNO, predicted and represented by using the Web-based tool SMART (v1.3)[7]. Regions of ARNO and mouse GNRP that Abergel *et al.*[1] propose are homologous are boxed. However, this region of GNRP instead contains a pleckstrin-homology domain (PH) and a REM domain that occurs N-terminal to some Ras guanine-nucleotide-exchange factor (RasGEF) domains; alternative names for the REM domain are RasGEFN domain, N domain and RasGN domain (the latter being used in the figure. The RasGEF REM-domain alignment in the latest version of SMART (v2.0; domain RasGN)[10] represents the full-length structure as shown in the SOS crystal structure. IQ is a short putative calmodulin-binding motif containing conserved isoleucine and glutamine residues.

the accuracy of many domain-homology predictions can be achieved by using data that is culled from available sequences and structures and statistically evaluated by standard methods.

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Author correction

In the article by Abergel *et al.* published in December 1998 (*TiBS* 23, 472–473), BLOCK I and BLOCK II were positioned incorrectly in Fig. 1. A corrected version of the figure is shown below.

Figure 1

Clustal W (Ref. 11) alignment of 13 Sec7-related sequences and five CDC25-related sequences. The first eight sequences (ARNO to GEA1) correspond to guanine-nucleotide-exchange factors (GEFs) that act on ADP-ribosylation factors (ARFs) ARF1 and ARF3, whereas the targets of the Sec7p, GNOM and TYL proteins are not known. The five mammalian GEF proteins captured in the search are shown in green. The 11 positions shown in red are strictly conserved (with one exception, RASGRF2_MM, where a Leu→Pro change is caused by a single T→C nucleotide change in the mRNA sequence). The 13 positions shown in blue are identical in all Sec7-related sequences. Positions corresponding to the consensus (>50% identity) in the Sec7 domain are shown in green. GenBank accession numbers follow (in parentheses): ARNO_HS (X99753); ARNO3_HS (AJ223957); CDC25_HS (L26584); CH-1_HS (M85169); Gea1p_SC (Z49531); GNOM_AT (U36433); GNRP_MM (L20899); GNRP_RN (X67241); GRP1_MM (AF001871); MER2p_SC (Z49531); RASGRF2_HS (AF023130_1); RASGRF2_MM (U67326); RIP1p_SC (U18530); SEC7A_RN (U83895); SEC7B_RN (U83896); SEC7C_RN (U83897); TYL_HS (X99688). AT, *Arabidopsis thaliana*; HS, *Homo sapiens*; MM, *Mus musculus*; RN, *Rattus norvegicus;* SC, *Saccharomyces cerevisae.*