Aromatic Interactions

The distribution of dihedral angles between two aromatic residues in globular proteins is shown in figure 1 of the Research Article by S. K. Burley and G. A. Petsko (*1*). It can provide evidence for the importance of specific interactions between aromatic rings only if it differs significantly from a random distribution. The expected distribution can be considered in terms of the angles between the normals to the two ring planes. Singh and Thornton (*2*) have pointed out that the distribution of this angle that would arise by chance varies as the sine of the angle and has a mean value of ~57°. The overall distribution in figure 1 of Burley and Petsko thus closely approximates a random distribution.

However, it is also necessary to consider the spatial displacement of the two aromatic rings, as measured by polar coordinates r, T_θ, and T_ϕ between ring centers [figure 2 in (*2*)]. A parallel, fully stacked arrangement ($P = 0$) can only occur for T_θ approaching 90°. When the P distribution is plotted for different ranges of this angle [figure 4 in (*2*)], two arrangements show significant deviations from random $62.5° < T_\theta < 90°$ (the fully stacked arrangement) and $45° < T_\theta < 67.5°$ (the moderately stacked arrangement). In the fully stacked arrangement the perpendicular interaction is clearly preferred and is in agreement with recent quantum mechanical calculations that show that the perpendicular interaction is energetically preferred. In the partially stacked arrangement the deviation from random appears to favor values of $P < 60°$, which is also consistent with quantum mechanically derived nonbonded potential calculations.

The cutoff criteria also need to be carefully defined in the analysis of aromatic interactions. Center-to-center distances differ for rings that are in van der Waals contact above one another and those that are side by side (3.4 to 6.8 Å). It is preferable for such nonspherical side chains to define contacting aromatic groups by closest atom-atom distances [allowing for probable errors (<1 Å) in the x-ray analyses] in order to arrive at an equal probability of contacts around the rings.

In conclusion, we wish to emphasize the importance of taking into consideration the available three-dimensional space and expected "random" distributions for such side chain interactions. A striking preference for perpendicular packing of aromatic rings is observed for a small subgroup in a special spatial displacement. Elsewhere energetic preferences and constraints imposed by packing of many hydrophobic residues in the protein core may give a slight preference for either the perpendicular or the parallel arrangement.

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Brain "Identifier Sequence"

In their report "Brain 'identifier sequence' is not restricted to brain: Similar abundance in nuclear RNA of other organs" (*1*), Owens *et al.* incorrectly assert (their reference 11) that the "identifier" (ID) family of rat repeated sequences (*2*) is completely divergent over the more 3′ located nucleotides from the 4D-12 rat repeated sequence (*3*). We reported that the 4D-12 sequence is a typical version of the ID sequences published by others (*2, 4*) and that transcripts of it were abundant in the nuclei of various rat cells, including those from liver and kidney (*3*). We also pointed out (*3*) that the ubiquitous nuclear distribution of 4D-12 (ID) transcripts contrasted with the finding of ID transcripts only in brain cytoplasm (*2*).

Figure 1 shows the alignment between the ID sequence in the p2A120 clone (*2*) used by Owens *et al.* (*1*) and the 4D-12 sequence (*2*), as well as two other members of the ID family (*4*). The sequence labeled B is cited by Owens *et al.* as a typical ID sequence (their reference 4). Although these sequences exhibit differences in the lengths and composition of their A-rich right ends, this is a typical feature of repeated interspersed mammalian DNA families (*5*) such as the ID family, and no region of "complete divergence" among these ID sequences is evident.

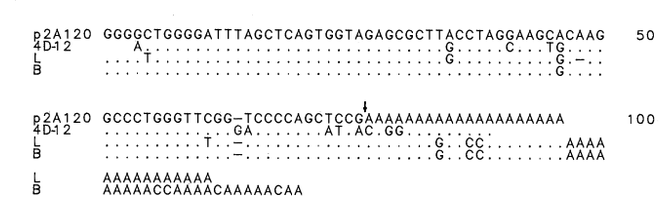

Fig. 1. Alignment among rat ID sequences. Only the ID portion of the p2A120 clone [without its 3′ oligo C track used for cloning in the Pst I site of the vector (*2*)] and of the DNA sequences reported in (*4*) (L and B) is shown. All of the sequence of the 4D-12 repeat is shown, but without its 5′ G- or 3′ C-tails that were used for cloning this sequence (*3*). The arrow indicates the beginning of the A-rich region, which is typically at the right end of members of interspersed repeated DNA families and which varies both in length and composition (*5*). The dots indicate where the sequences are identical; the dashes or letters indicate where they are not.

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Response: In the note included in reference 11 of our report (*1*) we did not indicate that clone 4D-12 described by Witney and Furano (*2*) cannot be regarded as a member of the "ID" repeat family in the rat genome. In fact we stated that Furano regards 4D-12 as a typical representative of the ID repeat family. We added the comment on 3′ end divergency only because in comparison to clone p2A120 and the common or consensus 82-nucleotide sequence arrived at by Sutcliffe *et al.* (*3*) the sequence of clone 4D-12 is different at the 3′ end. Within the 3′ region of the ID clone p2A120 and the 82-nucleotide common sequence the sequence CCCAGCTCCGAAAAA occurs (*3, 4*). In clone 4D-12, beginning after alignment of the common triplet *CCC*, the sequence . . .CAGCATCACAGG is found (*2*), which is divergent from the clone p2A120 that we used in our measurements. Perhaps we were overly cautious in raising this minor point for readers to consider. Of more importance and as we mentioned twice in our report is the observation by Witney and Furano that the 4D-12 cloned repeat hybridizes to nuclear RNA from several sources including liver and kidney (*2*), just as we found using the ID repeat in clone p2A120. Hence the determinations made by Witney and Furano and those contained in our report both point to rather ubiquitous transcription of the ID repeat in various rodent cells and organs.

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