

Sequence of rat RL/IF-1 encoding IKB β -like activity and comparison with related proteins containing notch-like repeats

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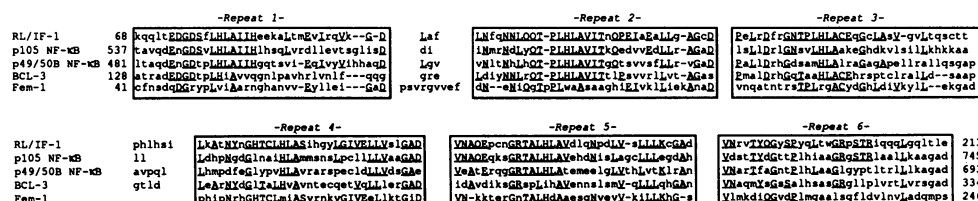
Previously, we identified an immediate-early gene, RL-14, rapidly induced in regenerating liver and mitogen-stimulated cells (1). Complete DNA sequence analysis of the full-length RL-14 clone corresponding to the 1.8 kb mRNA, showed that RL-14 encodes a 314 amino acid protein containing 5 notch-like repeats. RL-14, which we then designated RL/IF-1, regenerating liver inhibitory factor-1, is the rat homolog of human MAD-3 (2) and probably of chicken pp40 (3) which have IKB-like activity. IKB proteins are cytoplasmic inhibitors of p50/p65 NF-KB and Rel family transcription factors that mediate inhibition by binding to Rel and NF-KB subunits. Upon cellular stimulation, IKB is released from NF-KB and Rel which then can move to the nucleus and activate transcription (4, 5). RL/IF-1 and MAD-3 share 80% nucleotide and 90% amino acid homology, and RL/IF-1 and chicken pp40 protein share 63% nucleotide and 70% amino acid identity, including some nucleotides in the 3' untranslated region. We have demonstrated that RL/IF-1 has IKB β -like activity in that it inhibits the DNA binding of NF-KB, c-Rel and RelB, and is likely to be identical to IKB β (6, 7, 8).

In data bank searches RL/IF-1 and MAD-3 have greatest homology with notch-like repeat proteins related to the NF-KB family of transcription factors. These include the repeat region of p105, the precursor to the p50 subunit of NF-KB (9, 10, 11), and the precursor protein for p49 or p50B, an NF-KB-like protein (12). Two other highly related proteins are BCL-3, a repeat protein found at the chromosomal translocation break point in B cell tumors (13) and Fem-1, a *C. elegans* protein involved in sex determination (14). The alignments of RL/IF-1 with this group of proteins (Fig. 1) indicate that not only the consensus sequences in the repeats are similar, but the order of highly similar repeats is conserved. Although there are only five true repeats in RL/IF-1, there is the beginning of a sixth repeat which shares homology with the corresponding repeat in the other proteins. Within the repeat regions the overall amino acid identity of

RL/IF-1 with p105 NF-KB, p49/p50B NF-KB, BCL-3, and Fem-1 are 41%, 37%, 33% and 31%, respectively. Additionally, like RL/IF-1, both p105 NF-KB, p49/p50B NF-KB have an acidic carboxy terminus of unknown function. These findings suggest that this group of repeat proteins are derived from a common ancestor, and may have similar IKB-related functions. Much less similar are ankyrin, notch and other repeat proteins with structural roles (15). However, like ankyrin, it is likely that notch-like repeats in the IKB proteins are involved in the dimerization of IKB with Rel family members.

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Alignment between notch-like repeat regions of RL/IF-1, p105 NF-KB, p49/p50B NF-KB, BCL-3 and c-Fem-1. Identities are capitalized and underlined, and notch-like repeat regions are indicated.

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