The PEA3 Group of ETS-related Transcription Factors

Role in breast cancer metastasis

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Abstract

The ets genes encode eukaryotic transcription factors that are involved in tumorigenesis and developmental processes. The signature of the Ets family is the ETS-domain, which binds to sites containing a central 5’-GGAA/T-3’ motif. They can be sub-classified primarily because of the high amino acid conservation in their ETS-domains and, in addition, in the conservation of other domains generally characterized as transactivating. This is the case for the PEA3 group, which is currently made up of three members, PEA3/E1AF, ER81/ETV1 and ERM, which are more than 95% identical in the ETS-domain and more than 85% in the transactivation acidic domain. The members of the PEA3 group are activated through both the Ras-dependent and other kinase pathways, a function which emphasizes their involvement in several oncogenic mechanisms. The expression pattern of the three PEA3 group genes during mouse embryogenesis suggests that they are differentially regulated, probably to serve important functions such as tissue interaction. Although the target genes of these transcription factors are multiple, their most frequently studied role concerns their involvement in the metastatic process. In fact, PEA3 group members are over-expressed in metastatic human breast cancer cells and mouse mammary tumors, a feature which suggests a function of these transcription factors in mammary oncogenesis. Moreover, when they are ectopically over-expressed in non-metastatic breast cancer cells, these latter become metastatic with the activation of transcription of matrix metalloproteinases or adhesion molecules, such as ICAM-1.
1. INTRODUCTION

The ets genes encode a family of eukaryotic transcription factors that includes more than 30 members from sponges to humans\(^1\). They have been involved both in tumorigenesis and in a number of developmental processes. Members of this family were originally identified on the basis of a region of primary sequence identity with the protein product of the \(v\)-ets oncogene encoded by the \(E26\) (\(E\) twenty-six) avian erythroblastosis virus. This signature is the ETS-domain\(^3\), a domain of 85 amino acids structured as a winged helix-turn-helix structure and responsible for DNA-binding\(^1\). Many promoters have been characterized as containing active Ets-binding sites. For example, Ets proteins are involved in the regulation of the transcription of membrane receptors, growth factors or transcription factors\(^1\).\(^2\). Except for very limited examples, the specificity of an Ets protein to the regulation of gene transcription has not yet been established. However, this specificity could be at three levels: (1) the expression sites of the ets gene, (2) the DNA-binding specificity of the ETS-domain, and (3) the presence of specific domains required for protein-protein interactions. These factors can be subclassified primarily because of the amino acid conservation in their ETS-domains and, in addition, in the conservation of other domains generally characterized as transactivating.

2. THE PEA3 GROUP MEMBERS

This is the case for the PEA3 group, which is currently made up of three members, PEA3 (also called E1AF in the human or ETV4)\(^4\)-\(^6\), ER81 (also called ETV1 in the human)\(^7\)-\(^9\) and ERM (also called ETV5)\(^10\)-\(^12\), which are more than 95% identical in the ETS-domain and more than 85% in the 32 residue acidic domain, and almost 50% identical in the final 61 residues corresponding to the carboxy-terminal tail of the proteins (Ct)\(^13\). ERM and ER81 are more closely related to each other than PEA3, suggesting that a common ancestor of the three genes has undergone two successive duplications. As illustrated in Fig. 1, human \(erm\) gene is composed of 14 exons split into at least 65 kbp of genomic DNA\(^14\). Human \(etvl\) and human \(elaf\) are each composed of 13 exons covering more than 85 kbp and 19 kbp, respectively\(^15\)-\(^16\). The genomic organization of the ETS and the acidic domains of these genes is similar; i.e. they are both encoded by three different exon\(^14\)-\(^16\). Concerning their chromosomal locations in the human, \(erm\) is situated at position 3q27-q29\(^10\)-\(^11\), \(elaf\) at position 17q22\(^17\)-\(^18\) and \(etvl\) at position 7q21\(^8\).