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THE 37 LRP/P40 POLYPEPTIDE: A MULTIFUNCTIONAL PLEIOTROPIC MOLECULE INVOLVED IN TUMORIGENESIS AND METASTASIS

A REVIEW

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Abstract. A cDNA coding for a 37 kDa polypeptide has been the center of major interest since it is consistently up-regulated in several cancers in association with the metastatic phenotype of the lesion. Furthermore, this polypeptide displays intriguing multifunctional properties as it has been cloned both as the metastasis-associated 67kD membrane-associated laminin receptor precursor (37 LRP) but also as a cytoplasmic ribosomal-associated protein p40. Isolation of the gene coding for the 37 LRP/p40 peptide in humans and birds, analysis of their structures and extensive amino-acid comparison between available species sequences have brought new topological arguments in favor of a multifunctional role for this protein in cells. Indeed, both genes display characteristics of house-keeping genes and in particular of ribosomal protein -encoding genes. Comparison between all 37LRP/p40 amino-acid sequences identifies a particularly well conserved region in the center of the protein in all organisms. This central part of the protein is the only region similar to the parentally linked RS2 prokaryotic ribosomal protein. In contrast, the carboxy terminal end of the protein is highly variable in all organisms until the vertebrates appear. As vertebrates are the only organisms in which a 67 LR molecule has been clearly described, it is suggested that this region of the molecule supports a new function *i.e* the ability to be included into the 67 kD cell surface laminin receptor. This hypothesis is further sustained by the fact that the carboxy-terminal end of the protein is precisely encoded by the last two exons. An evolutionary scenario is proposed in which the 37 LRP/p40 molecule has always had a function as a ribosome-associated protein, encoded by the central highly conserved region. In the course of evolution, an additional function linked to the carboxy terminal end of the protein would have developed in organisms in which cell-matrix interactions became more complex.

Cancer, metastasis and the 67 kDa laminin receptor

Metastasis is the major cause of mortality and morbidity in cancer. Metastasis formation is a process which involves complex interactions between metastatic cells and the sur-

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rounding tissue. Indeed, in order to metastasize cancer cells have to aquire the ability to leave the initial tumor, migrate into the surrounding tissue, enter a blood or lymphatic vessel, survive in the blood stream or lymph and finally leave the vessel again to invade and proliferate within a target organ (Fig. 1). In the course of this process, metastatic cells have to several times cross the physiological inter-tissue barriers called basement membranes (CASTRONOVO,1993; FLUG & KÖPF-MAIER,1995). Therefore understanding of the interactions between basement membranes and cancer cells is of major interest since inhibiting this process could potentially lead to efficient treatment against this critical step in cancer development.

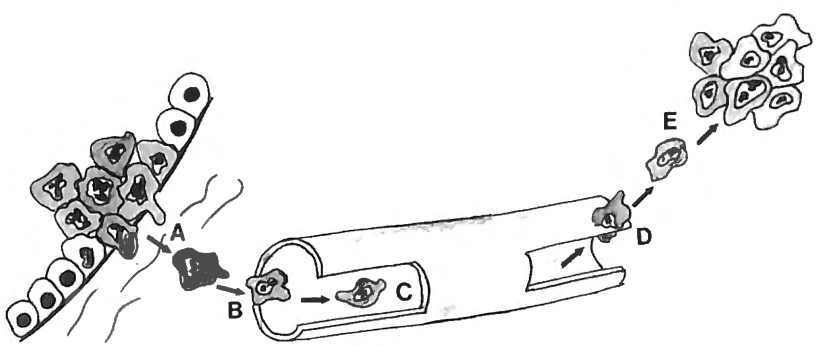

Fig. 1. – Schematic representation of the metastatic cascade. Cancer cells have to leave the initial tumor and migrate into the surrounding tissue (a), enter blood or lymphatic vessels (b), survive into the blood or lymph stream (c), leave the vessel (d), migrate to the target organ (e) and form a secondary colony.

Crossing of basement membranes by cancer cells has been schematically divided into three steps: attachment, degradation and migration (LIOTTA *et al.*,1986). Several laboratories have searched for cellular receptors which could play a role in the initial attachment step of cancer cells to one of the major components of basement membrane, laminin. The first molecule isolated which was able to bind to laminin is a molecule of 67 kD thereafter named the 67kD laminin receptor (67LR) (LESOT *et al.*,1983; MALINOFF & WICHA,1983; RAO *et al.*,1983). Since that time, several other molecules able to bind laminin have been isolated such as members of the integrin family and lectins (CASTRONOVO,1993). However, the 67 LR remains the center of major interest since it has been shown to be over-expressed in several solid tumors such as breast, colo-rectal, gastric and cervical carcinoma in correlation with the invasive and metastatic phenotype (CAMPO *et al.*,1992; CASTRONOVO *et al.*,1992; CIOCE *et al.*, 1991; GASPARINI *et al.*,1995; KONDOH *et al.*,1992; MARTIGNONE *et al.*,1992, 1993; PELLEGRINI *et al.*,1995; SOBEL,1993). The association between 67LR over-expression and cancer progression suggests that the 67 LR might play a role in tumor progression. Therefore, isolation and cloning of the 67LR coding gene and cDNA became a priority.

Cloning of the 37 kDa laminin receptor precursor cDNA

Cloning of the 67 LR encoding cDNA was initially performed using an anti-67 LR antibody which has the interesting functional property of blocking the adhesion of laminin onto the surface of cancer cells. This antibody has been used to screen a human umbilical vein cDNA expression library and led initially to isolation of an incomplete cDNA (WEWER *et al.*,1986). Further work resulted in isolation of a complete cDNA sequence from both mice and humans (RAO *et al.*,1989; YOW *et al.*,1988). Intriguingly, the length of this cDNA allows to encode a polypeptide of a deduced molecular weight of only 37 kD. This discrepancy between the size of the 67 LR and the size of the product encoded by its putative cDNA suggested post-translational modifications. The absence of potential N-glycosylation sites in the cDNA sequence as well as failure to stain the 67 LR with PAS and the maintenance of the 67 kD size of the molecule after neuraminidase, o-glycanase or Endo-F glycosidase treatment allow a glycosylation step to be eliminated as the major cause of size increase (CIOCE *et al.*,1993; LANDOWSKI *et al.*,1995). On the other hand, treatment of the 67 LR by reducing agents does not lead to a diminution of the 67 LR size, eliminating the hypothesis of a possible non-covalent multimeric molecule. Recently, it has been suggested that the 67 LR might be acylated by the fatty acids palmitate, oleate and stearate (LANDOWSKI *et al.*,1995). These fatty acid could be covalently associated with the protein via ester linkage suggesting that the 37 LRP can dimerize with itself or with another peptide to form the 67 LR. However, such suggestions still need further experimental evidence and the molecular mechanisms responsible for the increase in size of the 37 kD molecule into a 67 kD molecule remain unclear so far. Nevertheless, several experiments suggest a precursor/product relationship between the 37 kD molecule encoded by the cDNA and the 67 kD laminin receptor. Indeed, immunoprecipitation with antibodies directed against synthetic peptides derived from the 37 kD encoding cDNA allow precipitation of both the 37 kD and the 67 LR molecules. Further, pulse-chase experiments reveal the disappearance of a 37 kD polypeptide concomitant with appearance of the 67 LR (CASTRONOVO *et al.*,1991). Microsequencing of two peptides from the 67 LR gave a sequence of eight amino-acids identical to a portion of the 37 kD molecule (WEWER *et al.*, 1986). Finally, transfection of the 37 kD cDNA tagged with 6 additional histidines and with an artificially added phage epitope led to the recovery of a tagged 67 kD molecule which is able to bind laminin and is localized at the cell surface (MONTUORI *et al.*, pers. comm.). These observations are all consistent with a precursor/product relationship between the two molecules and led to the 37 kD molecule being called the laminin receptor precursor (37 LRP).

Interestingly, the cDNA coding for this 37 LRP molecule has been cloned by others as a cytoplasmic protein, in particular as the mouse ribosome-associated protein p40 (MAKRIDES *et al.*,1988; ROSENTHAL & WORDEMAN,1995; TOHGO *et al.*, 1994). In addition, search for homology between sequences from an archebacterium and all published sequences reveals that the 37 LRP deduced amino-acid sequence is homologous at 40% with the prokaryotic ribosomal protein RS2 (OUZONIS *et al.*,1995). This new putative role for the 37 LRP cDNA raises several questions and invites further investigations in order to better understand the role of this intriguing molecule in cells. In that perspective we decided to clone the gene coding for this 37LRP/p40 cDNA in order to better understand

its position either in a house-keeping gene family or as a tightly regulated gene. In addition we have conducted an extensive amino-acid sequence comparison between 37 LRP/p40 cDNA from all species already described and a new sequence that we have recently cloned in the laboratory from chicken spleen cDNA (CLAUSSE *et al.*,1996). This avian sequence is consistant with available mammalian sequences and thus extends the comparison more widely within the vertebrates.

The 37 LRP/p40 gene family

The 37 LRP/p40 gene has been cloned both from human and chicken DNA. The cloning of the human gene has been hampered by the presence in the human genome of around 26 copies of pseudogenes. These pseudogenes have been characterized in our laboratory (JACKERS *et al.*,1996a). They are highly homologous to the active gene but are interrupted by several stop codons. These pseudogenes have no intronic sequence, they are terminated by a polyA-tail and flanked by direct repeated sequences. These characteristics suggest that they probably arose by retroposition events. A PCR-based strategy produced a specific intronic probe and allowed us to specifically isolate the active human gene copy (JACKERS *et al.*,1996b). By contrast, the chicken appears to be the only organism in which the 37LR/p40 gene exists as a single copy. We were therefore able to isolate in parallel by a classical cloning technique the avian version of the 37LRP/p40 active chicken gene (CLAUSSE *et al.*,1996). Both genes are spread onto 6 kb of genomic DNA and are split into 7 exons with an initial short non-coding exon (Fig. 2). They have no classical TATA-box. Rnase protection and primer extension experiments reveal at least two transcriptional start sites located in a pyrimidine-rich tract. These features are characteristic of house-keeping genes and more particularly of genes encoding ribosomal proteins. Interestingly, in the intron 4 the human gene contains a region coding for a small nucleolar RNA E2. Finally, chromosomal hybridization localized the human 37 LRP/p40 gene to 3p21.3 band, a chromosomal locus frequently involved in rearrangements associated with cancer.

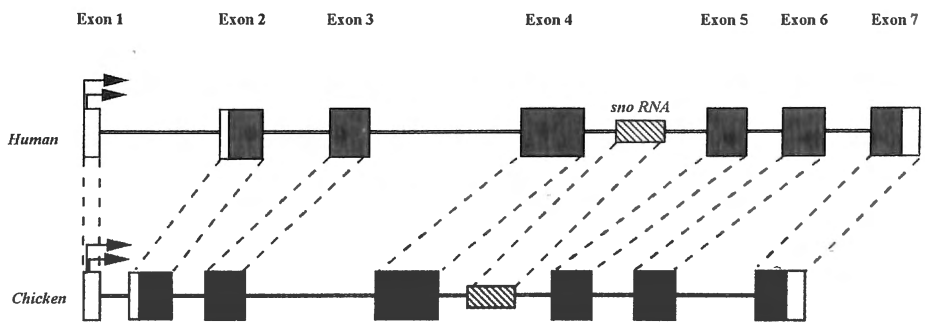

Fig. 2. – Schematic representation of the human (a) and chicken (b) gene structure. Exons are depected by boxes. Mutltiple transcriptional start sites are represented by horizontal arrows. Coding region is hatched. The position of the human encoding small nucleolar RNA sequence is represented by a grey box.

The 37 LRP/p40: a multifunctional protein

The 37 LRP cDNA has been cloned in 17 different species including mammals such as human, rat, bovine, mouse, and hamster, birds, insects, urchin, hydra, higher plant as arabidopsis, fungus and yeast. Comparison of the deduced amino-acid sequences from each cDNA reveals an extremely high degree of conservation throughout evolution. However, when these different sequences are carefully aligned to each other it appears that the conserved region is restricted to the central part of the molecule from amino-acid 20 to amino acid 209 whereas the carboxy-terminal end of the molecule varies between species until the appearance of vertebrates (CLAUSSE *et al.*,1996) (Fig. 3). Indeed, since birds and mammals diverged in evolution, *i.e.* 300 millions years ago, this carboxy-terminal end of the protein has been extremely well conserved. It appears that a high selective pressure has been applied to this region of the protein in vertebrates only. It is therefore tempting to speculate that, in vertebrates, a specific function might be located in that region of the protein which would explain this contrasting «sudden» sequence «freezing» arising in vertebrates. As a 67LR molecule related to the 37LRP/P40 has been clearly described in vertebrates only, we suggest that this carboxy-terminal end of the molecule would be responsible for the yet undefined post-translational events leading to the 67 LR. In favor of this hypothesis is the alignment of the gene structure with sequence comparison. Indeed, this superposition reveals that this vertebrate conserved carboxy-terminal region corresponds exactly to exons 6 and 7 (Fig. 4). The existence in vertebrates of a specific function in that particlar region would be in accordance with the widely held theory that exons are function depositary elements serving as basic building blocks to diversify and modulate protein function during evolution (BLAKE,1979; Blake,1983). To go further in this analysis, we have aligned the parentally linked prokaryotic RS2 ribosomal protein sequences with the 37 LRP/p40 amino-acids deduced sequences (DAVIES *et al.*,1992). To our surprise, it appears that although the RS2 proteins are longer in size than the central conserved part of the 37 LRP/p40 (257 and 209 amino-acid respectively), the best alignment was obtained by creating a gap of 49 amino-acids in the 37LRP/P40 in order to confine the entire RS2 sequence in this central conserved region (Fig.4). Moreover, it appears that the two consensus RS2 motif signatures described in RS2 proteins are present in all 37LRP/P40 sequences available with the only exception of one tryptophane. These observations led us to suggest that the 37LRP/P40 molecule might play two functions in cell: a cytoplasmic ribosomal-associated function played by the central part of the protein, conserved since archebacteria and efficient in all organisms, and since vertebrates, a cell surface role as a laminin receptor when incorporated into the 67 kD laminin receptor via its carboxy terminal end. We proposed an evolutionary scenario for this molecule: originally involved in translation, a vital function for cell biology, the protein could have aquired new properties *i.e.* as a building block of a receptor, in the course of evolution to accomodate the new extracellular matrix protein, laminin. This potential multifunctional role for a protein is not unique. Indeed, a rather similar situation has been described for eye lens crystalline in which one gene product has either a sructural role in the refractive properties of the lens or a house-keeping enzyme role when associated in dimeric molecule (HENDRICKS *et al.*,1988; WISTOW *et al.*,1988). Other examples illustrate possible multiple functions for ribosomal protein. Indeed, when associated in a multimeric protein by trans-

glutamination, the S19 ribosomal protein would play the role of a chemotactic agent for macrophages at the site of inflamation (NISHIURA *et al.*,1996). In the same perspective, galectin-3 a human lectin originally isolated as a cell surface laminin binding protein has lately been described as a nuclear protein involved in mRNA splicing mechanism (DAGHER *et al.*,1995). Such a dual fate for a single gene product might constitute a parsimonious means of protein function diversification during evolution.

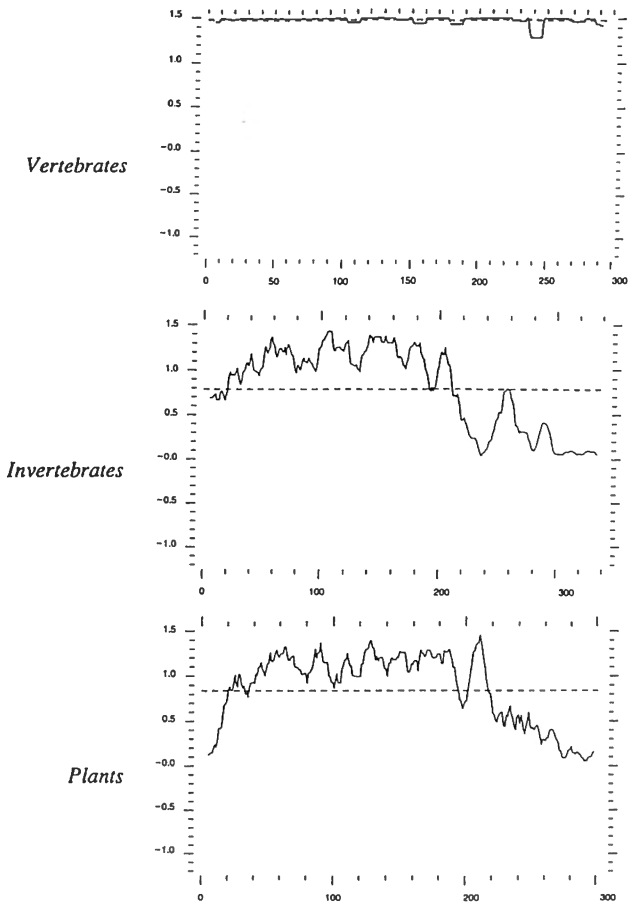

Fig. 3. – Amino acid similarity between all 37 LRP/p40 cDNA protein sequences deduced from all species described. Similarity between amino-acis (vertical axis) has been calculated for each amino-acid position (horizontal axis) according to the Burgess table by the GCG programm using the Plotsimilarity function after alignment with Pileup function (DEVEREUX *et al.*,1984). Maximum similarity of 1.5 represents identical amino-acids. The mean value is represented by a dotted line crossing the graph. Homology is therefore significant when the line is above the mean value whereas no significant homology is when the value is below the mean value. The vertebrate group includes chicken, bovine, mouse, hamster, rat and human sequences. Invertebrates include the insect *Drosophila*, two urchin species *Urechis caupo* and *Tripneustes gratilla*, the hydra *Chlorohydra viridissima* and the cestode *Echinococcus granulosus* sequences. Plants include the higher plant *Arabidopsis thaliana*, the fungus *Pneumocystis carinii*, and the yeast *Saccharomyces cerevisiae.*

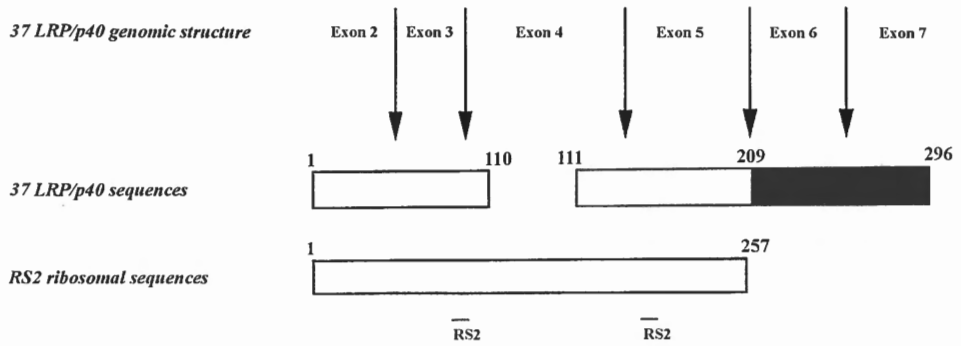

Fig. 4. – Schematic alignment of 37 LRP/p40 sequences with parentally linked RS2 ribosomal protein sequences. Position of the exons are shown at the top of the figure relative to the deduced amino-acids sequences from 37 LRP/p40 sequences. The hatched box represents the region conserved only in vertebrates. The gap in the 37 LRP/p40 sequences is created to obtain the best alignment with RS2 sequences shown below. RS2 signature positions are represented by horizontal lines under the scheme. Numbers on top of each sequence reflect amino-acid positions.

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