COMMENTARY

Soluble vertebrate lectins: ubiquitous but inscrutable proteins

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Introduction

It is not widely appreciated that lectins are at least as abundant in vertebrate as in plant tissues. The literature is muddied by a confusion over the definition of a lectin and by a wide variety of conflicting nomenclature. Lectins have also rather lacked credibility because in very few cases has there been a clear demonstration of the functionally important interaction of a lectin with its endogenous carbohydrate ligand. Nevertheless, it is now clear that vertebrate lectins are involved in a wide diversity of cellular activities. While this undoubtedly makes them very important molecules, it also makes it difficult to delineate their individual functions. Lectins were originally defined as multivalent, non-immunoglobulin, carbohydrate binding molecules (Goldstein *et al.* 1980), operationally defined by their ability to agglutinate cells bearing appropriate saccharide structures. More recently it has seemed appropriate to include proteins with a single carbohydrate binding site (Barondes, 1988; Gabius, 1991) and this pragmatically modified definition is becoming generally accepted. This interpretation extends the term lectin to a large number of other molecules with a well-characterised carbohydrate binding activity that were not originally isolated as lectins, for example fibronectin, and results in a broader picture of the great diversity of lectin function.

In vertebrates several lines of investigation have converged on lectin studies. There has been much interest in the functions of the diverse oligosaccharide structures carried by glycoproteins and glycolipids. Carbohydrates are ideally suited to be recognition signals as the great variety of possible saccharide structures attainable within a single sequence confers on oligosaccharides an enormous potential for encoding biological information. Structural analysis has shown that changes in oligosaccharide structure are concomitant with tissue development, cellular differentiation and various pathological states, suggesting that they could play a physiologically important role. These observations have spurred on the search for specific carbohydrate binding ligands, lectins. Conversely, many molecules under study for different activities have been discovered, either experimentally or by sequence comparison, to contain carbohydrate binding sites. More recently, saccharide structures *within* the cell have been recognised (Hart *et al.* 1989), providing possible ligands for lectins intracellularly also.

Two main classes of lectins have emerged in vertebrates (Drickamer, 1988): C-type lectins have a Ca^{2+}-dependent carbohydrate binding activity and contain a carbohydrate recognition domain (CRD) homologous to that first identified in the asialoglycoprotein receptor. Many molecules in this category were first identified by virtue of this sequence homology and the functional significance of their saccharide binding has yet to be determined. The C-type CRD has been detected in a wide variety of membrane-bound and soluble molecules (Drickamer, 1988); for example, mannose binding proteins in liver and serum, lung surfactant apoprotein SP28–36, the lymphocyte receptor for the Fc portion of IgE, the proteoglycan core in fibroblasts and cartilage, and in the structurally related, blood cell adhesion molecules PADGEM/GMP-140, ELAM-1 and gp90MEL. These three molecules are of particular significance to 'lectinologists' because the physiological carbohydrate ligands of two of them have recently been identified (reviewed by Brandley *et al.* 1990; Springer and Lasky, 1991; Feizi, 1991). This work has been greatly stimulated by the possible therapeutic applications of carbohydrate analogues in modifying the interactions of blood and vascular cells and illustrates the powerful potential of combining the modern techniques of cell and molecular biology with structural and immunological analysis.

In the second type of vertebrate lectin, saccharide binding is divalent cation independent. The experimentally determined requirement for thiol reducing agents to maintain saccharide binding activity *in vitro* suggested the term S-type lectins. These lectins do not appear to be glycosylated and those characterised to date can be described as soluble proteins, since they can be isolated from cells and tissues without recourse to detergents. Many S-type lectins share a specificity for β-galactoside residues and belong to a structurally related family of proteins, which have also been termed: electrolectins, galaptins, lactose lectins, carbohydrate binding proteins, S-lac (soluble lactose binding) lectins and gal-lectins; names that reflect their varied history. This Commentary concentrates on these lectins and although it seems unlikely that any generic term for these lectins will become generally accepted until their endogenous ligands and physiological functions are determined, for the sake of clarity and brevity I will use the term galaptin to refer collectively to members of this family, while using the nomenclature of specific investigators in referring to experimental data.

Key words: lectins, galaptins, carbohydrates.

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What are galaptins?

Current data suggest that there are at least four main types of galaptin. These lectins have overlapping saccharide specificities; they can all be isolated from cell lysates by affinity chromatography on immobilised lactose and, where haemagglutination activity has been demonstrated, it is inhibitable by lactose. The lectins, however, demonstrate a much higher affinity for the dimeric structure β-galactose-(1–4)-*N*-acetylglucosamine, *N*-acetyllactosamine (Leffler and Barondes, 1986; Sparrow *et al.* 1987; Abbott *et al.* 1988) and for the repeating unit [-β-galactose-(1–4)-β-*N*-acetylglucosamine-(1–3)]$_n$ the poly-*N*-acetyllactosamine sequence, which is the major component of polylactosaminoglycan chains, PLAG or LAGs (Merkle and Cummings, 1988). The possibility that galaptins are endogenous ligands for LAGs is particularly interesting, as these oligosaccharides are developmentally regulated, have been implicated in many important morphogenetic and developmental processes (Thorpe *et al.* 1988; Fenderson *et al.* 1990) and are becoming the focus of attention in these fields. Laminin and lysosomal-associated membrane proteins, LAMPS, are major carriers of LAGS and specifically bind the 14×10^3 M_r galaptin (Zhou and Cummings, 1990; Do *et al.* 1990). Galaptins are also structurally related, as demonstrated by sequence analysis or inferred by immunological cross-reactivity. It is easiest to distinguish the different galaptins by their molecular mass as 14×10^3 M_r, $16–22\times10^3$ M_r, $29–35\times10^3$ M_r and 67×10^3 M_r lectins, as summarised in Table 1.

The most abundant, and probably the most widely studied protein is the 14×10^3 M_r lectin first described in the electric organ of the electric eel (Teichberg *et al.* 1975) and then investigated extensively in chicken and mammalian tissues. Amino acid and cDNA sequencing has revealed a strikingly high degree of conservation of sequence between species; the bovine, rat and mouse 14×10^3 M_r lectins have 87–90% identity with their human counterpart. This has been taken to indicate that the lectin must have important physiological functions. Sequence analysis of the $29–35\times10^3$ M_r galaptin has also shown a great conservation of structure between species and an area of striking homology with 14×10^3 M_r lectin sequences has indicated which residues probably combine to form the saccharide binding site (see Fig. 1). Amino acid and nucleotide data are collated in a recent review (Harrison, 1991). Another probable member of this family is the 67×10^3 M_r elastin receptor, which is cross reactive with anti-14×10^3 M_r galaptin antibodies (Hinek *et al.* 1988). Galaptins of $16–22\times10^3$ M_r have been isolated from 3T3 fibroblasts (Roff and Wang, 1983) and rat (Cerra *et al.* 1985) and human lung (Sparrow *et al.* 1987). In addition to the four species of galaptin summarised in Table 1 there may also be a number of closely related protein species in certain tissues. For example, nine different lactose binding lectins were purified from rat intestine by affinity chromatography and ion-exchange chromatography. These included the 14×10^3 M_r and $29–35\times10^3$ M_r lectins. Some of the other seven lectins reacted with anti-galaptin antisera and N-terminal sequencing of the more abundant lectins with a free N terminus showed some homology and in one case complete identity with internal sequences of the $29–35\times10^3$ M_r lectin. It seems that the galaptin carbohydrate recognition domain, or CRD, like that characteristic of C-type lectins, is incorporated into a number of different proteins. Genomic analysis in chicken (Ohyama and Kasai, 1988) and man (Gitt and Barondes, 1991) has shown that the 14×10^3 M_r lectin is encoded by four exons, one of which contains the putative CRD sequence motif shared by the 14 and $29–35\times10^3$ M_r lectins (see Fig. 1). The gene structure therefore supports the concept of a mobile self-contained CRD. The similar yet distinct binding specificities of the different galaptins probably reflect both sequence divergence within the CRD and the influence of the rest of the protein structure.

Table 1. *The family of soluble β-galactoside-specific lectins*

14×10^3 M_r lectin

Structure: complete cDNA/amino acid sequence of human, mouse, rat, bovine and chicken lectin now available (collated by Harrison, 1991)
Termed: electrolectin, 14 kD galaptin, CBP13.5, RL 14.5, HL-14, CLLI and II
Localization: abundant at times of major tissue organization in embryonic development (Catt *et al.* 1987; Beyer and Barondes, 1982). In adult tissues prevalent in lung, skin, bone marrow and intestine (Harrison *et al.* 1984; Beyer and Barondes, 1982)
Proposed functions: growth factor (Wells and Mallucci, 1991)

$16–22\times10^3$ M_r lectin

Structure: undetermined, some cross-reactivity with other anti-galaptin antisera
Termed: CBP16, RL-18, HL-22
Localization: detected in immature liver, heart and muscle, also prevalent in adult lung (Cerra *et al.* 1985) and fibroblasts (Roff and Wang, 1983)
Proposed functions: none as yet
N.B. in rat intestine 9 distinct lectins of $14–19\times10^3$ M_r have been detected, suggesting that a greater diversity of galaptins may be present in some tissues

$29–35\times10^3$ M_r lectin

Structure: complete cDNA/amino acid sequence of human, mouse and rat now available (collated by Harrison, 1991)
Termed: CBP35, RL-29, HL-29, Mac-2, IgE BP, LBP
Localization: detected in a number of embryonic tissues and also in fibroblasts, macrophages, lymphocytes and adult lung (Crittenden *et al.* 1984; Cerra *et al.* 1985)
Proposed functions: component of hnRNP particles, CBP35 (Laing and Wang, 1988), macrophage laminin receptor, Mac-2 (Woo *et al.* 1990), lymphocyte IgE receptor, εBP (Robertson *et al.* 1990)

67×10^3 M_r lectin

Structure: undetermined, cross-reactive with anti-14×10^3 M_r galaptin antisera
Termed: 67×10^3 M_r elastin/laminin binding protein
Localization: prevalent in lung, chondroblasts (Hinek *et al.* 1988), ligamentum nuchae fibroblasts (Mecham *et al.* 1989*a*) and tumour cells (Mecham *et al.* 1989*b*)
Proposed function: bifunctional component of elastin and laminin receptor complex (Mecham *et al.* 1991)

Selected data and references are presented in this table to illustrate and summarise the different types of soluble β-galactoside-specific lectin (galaptin) that have been characterised to date. Further details and more extensive references are given in a recent review (Harrison, 1991)

What do they do?

There is now extensive literature reporting the activity of galaptins in a number of different tissues and processes, a diversity of reports that illustrates the widespread importance of lectins in cell biology. For example, galaptins are involved in embryonic development, connective tissue regulation, organisation of the nervous system, tumour development and immune regulation. Investigations in these systems have recently been reviewed in some detail (Harrison, 1991). It is apparent that galaptins are involved in basic biochemical functions, important to all cells but particularly prominent in certain situations. There are some aspects of their activities that are unusual

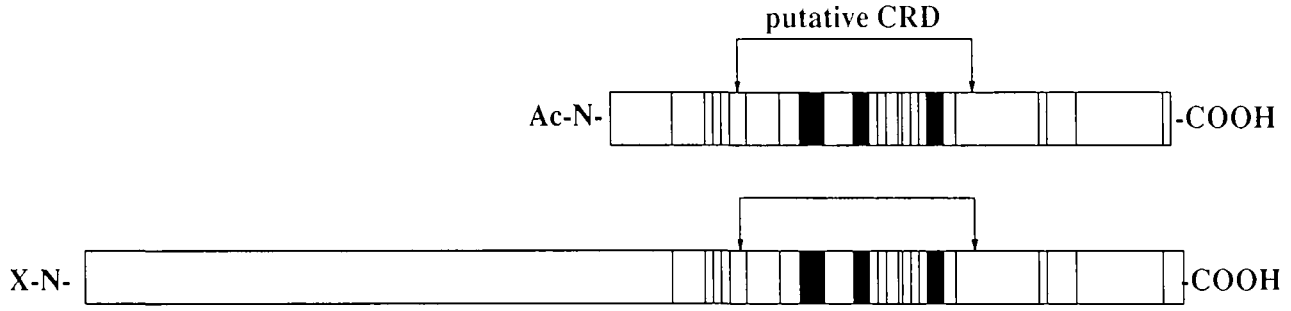

Fig. 1. Structure of the $14\times10^3 M_r$ and $29–35\times10^3 M_r$ galaptins. Diagrammatic representation of the amino acid sequences of the $14\times10^3 M_r$ and $29–35\times10^3 M_r$ galaptins. Residues identical in the consensus sequences for each lectin are represented as vertical bars. The arrows show the extent of the putative carbohydrate recognition domain (CRD) suggested by sequence homology and the exon structure of the $14\times10^3 M_r$ lectin gene.

and to accommodate them we must modify some current conceptions of cell biology.

While the C-terminal domain of the $29–35\times10^3 M_r$ lectin is homologous to the galaptin CRD the N-terminal domain comprises a repeated sequence strikingly conserved between species, which has not yet been identified in any other protein. However, some similarities to the proteins of heterogeneous nuclear ribonucleoprotein particles, hnRNPs, were noted (Jia and Wang, 1988). These particles are thought to be involved in the splicing, packaging and nuclear–cytoplasmic transport of mRNA in conjunction with small nuclear ribonucleoproteins, snRNPs or snurps. In a comprehensive series of experiments, John Wang and his colleagues have demonstrated that in 3T3 fibroblasts the $29–35\times10^3 M_r$ lectin, CBP35, is indeed a component of hnRNPs (Laing and Wang, 1988); more than 90 % cytosolic CBP35 is in RNP complexes. The nuclear–cytoplasmic shuttling of CBP35 is probably regulated by a cyclic phosphorylation analogous to the release of the transcription factor NF-κB from its cytoplasmic anchor by protein kinase C (Cowles *et al.* 1990). Subsets of hnRNP proteins may mediate the post-transcriptional control of specific RNAs and the transient exposure of shuttling proteins to the cytoplasm could provide a mechanism for the cytoplasmic regulation of the nuclear concentrations of these proteins. In response to serum stimulation, increased gene transcription results in an early (1–3 h) rise in CBP35 mRNA levels (Agrwal *et al.* 1989) and the unphosphorylated nuclear form of CBP35, which is barely detectable in quiescent cells, increases dramatically. CBP35 could therefore, play a central role in coordinating the cells' proliferative response to serum. The function of the saccharide binding capacity of CBP35 in this context remains undetermined. The galaptin in hnRNPs can bind to immobilised oligosaccharides, co-isolating the other hnRNP components as a unitary structure. This suggests that the unusual N-terminal domain may regulate association with other hnRNP components whereas the C-terminal CRD may have an as yet undetermined regulatory role in hnRNP activity.

In addition to its intracellular activities, CBP35 is also detectable at the cell surface. In fact, in the monocyte–macrophage cell lineage the $29–35\times10^3 M_r$ galaptin was first identified as a cell surface differentiation antigen and termed Mac-2 (Ho and Springer, 1982; Cherayil *et al.* 1989). Mac-2 synthesis is massively upregulated in inflammatory macrophages where it was recently identified as the major laminin binding protein (Woo *et al.* 1990). Adherence of stimulated macrophages to laminin has been shown to involve the integrin laminin receptor $\alpha_6\beta_1$ *in vitro* (Shaw *et al.* 1990) but the interaction of cell surface and secreted Mac-2 with the abundant LAG chains on laminin could act to stabilize interactions with the basement membrane *in vivo*. The $29–35\times10^3 M_r$ galaptin has also been identified as the major IgE-binding protein, ϵBP, in rat basophilic leukaemic cells (Albrandt *et al.* 1987), where its expression seems to be related to lymphocyte differentiation. The functional significance of the lectin's affinity for certain glycoforms of IgE is uncertain. If ϵBP were secreted, as Mac-2 has been reported to be, it could augment IgE-dependent mast cell activation (Robertson *et al.* 1990).

Clearly, much remains to be established concerning the activity of the $29–35\times10^3 M_r$ galaptin in different cell types. Nevertheless, the reports summarised above provide strong evidence that the *same* protein can perform multiple functions in all areas of the cell and its environs. Since one can envisage situations in which each function could be crucially important, there must exist mechanisms whereby the cell cannot only regulate the synthesis of CBP35/Mac-2/ϵBP but also control its cellular localization and activity. Post-translational modifications could provide such regulation and enable different cell types to respond appropriately to their individual environmental circumstances. The probable role of phosphorylation in the nuclear–cytoplasmic shuttling of CBP35 has already been described.

The $67\times10^3 M_r$ galaptin has an important extracellular function as a cell surface elastin receptor (Mecham *et al.* 1989*a*) and laminin receptor (Mecham *et al.* 1989*b*). It is a bifunctional protein with a β-galactoside binding site and a protein binding site. Lactose dramatically decreases the affinity of the receptor for both elastin and laminin whereas attachment of the receptor to the cytoskeleton increases its affinity for these ligands (Mecham *et al.* 1991). Lactose has been shown to inhibit elastic fibre formation in chondroblast cultures, illustrating the importance of these interactions (Hinek *et al.* 1988). The organisation of the extracellular matrix can therefore be regulated not only by the synthesis and secretion of matrix molecules and their surface receptors but also by the interaction of as yet uncharacterised, endogenous carbohydrate ligands with the $67\times10^3 M_r$ galaptin/receptor. Since the extracellular matrix plays such an important role in the regulation of cellular differentiation, it is not surprising that a complex network of multiple interactions is responsible for its organisation. A monoclonal antibody that blocked the binding of laminin to a $67\times10^3 M_r$ receptor was used to isolate a putative laminin receptor cDNA clone (Wewer *et al.* 1986; Rao *et al.* 1989). Recently a

$67\times10^3 M_r$ laminin receptor probe was also used to isolate an elastin receptor clone (Grosso *et al.* 1991). The cDNA clones, however, encode a highly conserved $33\times10^3 M_r$ cytoplasmic protein that has no sequence homology with galaptins. Furthermore, *in vitro* translation of the putative elastin receptor clone produces a protein that does not bind elastin and is not recognised by anti-$67\times10^3 M_r$ receptor antibodies. The relationship of this $33\times10^3 M_r$ protein to the $67\times10^3 M_r$ receptor is therefore uncertain at present.

The $14\times10^3 M_r$ galaptin, though probably the most abundant and the most studied, has remained the most inscrutable. Interest in galaptins has largely been maintained by the strong temporal association of the $14\times10^3 M_r$ galaptin with differentiation and embryonic development, but unlike the $29–35\times10^3 M_r$ and the $67\times10^3 M_r$ lectins, investigations of its structure, cellular location or regulation have not suggested a function. In the light of the multiple functions of CBP35 both intra- and extracellularly, the opposing proposals that the $14\times10^3 M_r$ lectin might function within the cytoplasm (Chaudhuri *et al.* 1988; Powell, 1988) or in the extracellular matrix (Barondes, 1984) no longer seem mutually exclusive. However, a mechanism for its secretion, as with Mac-2/ϵBP, remains to be determined. cDNA cloning has shown that the $14\times10^3 M_r$ galaptin has no hydrophobic leader sequence and immunocytochemical studies have never localised the lectin to the Golgi or any other cytoplasmic vesicle. Recent studies have shown that in differentiating muscle cultures the $14\times10^3 M_r$ lectin is concentrated just below the myotube surface and is released into the medium inside large vesicles that bleb off from the myotube (Cooper and Barondes, 1990). The term ectocytosis has been suggested to describe this novel process, which may, however, be restricted to muscle cells and has not been shown to occur *in vivo*. In considering this problem in other cell types, where the $14\times10^3 M_r$ galaptin is observed diffusely distributed throughout the cytoplasm, it is notable that the galaptin has many molecular characteristics in common with other secretory proteins lacking N-terminal hydrophobic sequences (Muesch *et al.* 1990). These proteins are not glycosylated and they appear to be present at high concentrations free in the cytosol. They are not secreted by all cell types and may be released only slowly. Some contain cysteines but no disulfide bridges. Notable in this family are the cytokines, interleukin-1, the fibroblast growth factors and the lipocortins, all of which exert profound effects extracellularly. Interestingly, a specific saccharide binding activity has been observed in recombinant interleukin-1α (Muchmore and Decker, 1987). Moreover, in the light of many reports that saccharides can modulate immune reactivity *in vitro*, the authors proposed that a number of cytokines would ultimately be shown to have a similar lectin-like activity. The mode of transport of these proteins across the plasma membrane is unknown, but the recent characterisation of a novel mechanism of protein export in bacteria has suggested a possible route. In Gram-negative bacteria, a family of structurally related ATP-driven transporters translocate various toxins and other proteins directly into the extracellular environment. In mammalian tissues, the phenomenon of multi-drug resistance in cancer cells has been shown to result from the expression of a single protein known as P-glycoprotein, encoded by the gene termed Mdr 1. Striking sequence homology between *Escherichia coli* HylB, the ATP-driven translocator of α-hemolysin, and the mammalian P-glycoprotein, first suggested that the normal function of the Mdr 1 gene product might be in the translocation of certain proteins across the plasma membrane (Gerlach *et al.* 1986). This hypothesis has recently been supported by the characterisation of a similar secretory mechanism in *Saccharomyces cerevisiae*, where the STE6 gene product is the ATP-driven transporter of the mating pheromone **a**-factor. Ste6 is closely related in sequence and structure to the P-glycoproteins, and establishes a link between protein export in prokaryotic and other eukaryotic cells (McGrath and Varshavsky, 1989; Kuchler *et al.* 1989). Furthermore, molecular biology has recently revealed that these substrate-dedicated ATP-driven protein translocators, may be quite widespread in the plasma membranes of eukaryotic cells (Kuchler and Thorner, 1990). A number of gene products closely related to Mdr1 have been identified, including the protein, CFTR, encoded by the gene implicated in the pathology of cystic fibrosis. The various substrates transported by this family of translocators remain to be determined. Clearly, the cytokines discussed above could constitute an interesting family of substrates in which galaptins might be included. It has been suggested that the activities of the ATP-dependent unfolding and refolding enzymes, the 'heat shock' proteins, may be required to modify substrates for transportation (Kuchler and Thorner, 1990), thereby introducing yet another control point in the regulation of secretion. It also seems likely that some form of post-translational modification may target proteins for secretion. For example, it has been estimated that perhaps 10–50% of cellular proteins may carry some kind of lipid modification that can dramatically affect their cellular localization (Magee, 1990). **a**-Factor is in fact a modified peptide, bearing a farnesyl moiety on its methylated C-terminal cysteine (Anderegg *et al.* 1988).

As the $14\times10^3 M_r$ galaptin shares many properties with peptide growth factors it seemed apposite when a growth factor secreted by mouse embryonic fibroblasts (MEFs) in serum-free medium was recently identified as the $14\times10^3 M_r$ lectin (Wells and Mallucci, 1991). The galaptin, termed murine β-galactoside binding protein, mGBP, was shown to inhibit MEF growth *in vitro*, acting as both a cytostatic factor, arresting MEFs in G_0, and as an inhibitor of cell replication, preventing the traverse of cells from G_2 into cell division. Identification of the $14\times10^3 M_r$ galaptin in this guise suggests many new lines of investigation. In these experiments mGBP was isolated from conditioned media and therefore constituted the secreted form of the protein. It is not known whether this form receives some type of post-translational modification, but the lack of sensitivity of the lectin to oxidation in these experiments suggests that this may be the case. Although growth inhibitory in these experiments, the $14\times10^3 M_r$ galaptin may prove, like other growth factors, to be multifunctional. TGFβ for example can act in a cell-type-specific manner to either promote or inhibit proliferation, differentiation and chemotaxis (Roberts *et al.* 1990). This seems most likely, since the temporal regulation of the lectin, which is particularly prominent at times of embryonic tissue organisation (Catt *et al.* 1987), has been directly correlated with erythropoiesis (Harrison and Catt, 1986) and myogenesis (Barondes and Haywood-Reid, 1981) but also with decreased cellular proliferation in the postnatal lung (Clerch *et al.* 1987; Powell and Harrison, 1991). The mechanisms of action of growth factors are not well understood at the molecular level (see e.g. Cross and Dexter, 1991) but a general pattern involves the interac-

tion of exogenous factors with specific cell surface receptors. The role of galaptin–saccharide binding in this interaction remains to be determined and could involve appropriate carbohydrate ligands, acting either directly or as regulatory modulators of galaptin binding. It has recently become apparent that some growth factors may have intracellular activity also (see Cross and Dexter, 1991), a concept particularly interesting with respect to galaptins, which have many structural features characteristic of intracellular proteins. These various activities could be integrated and regulated by alternative gene transcription or translation as well as by post-translational modifications. There are indications of a second, closely related form of the $14\times10^3 M_r$ lectin gene in humans (Gitt and Barondes, 1986; Gitt and Barondes, 1991).

Where to now?

Although the precise functions of galaptins have yet to be established, it is clear that their varied activities have a bearing on many areas of cell biology that are currently revealing new insights into the regulation of growth and differentiation. Many of their characteristics exemplify points of newly recognised importance. They constitute a family of proteins that combine a β-galactoside-specific CRD with other functional domains. Moreover, the $14\times10^3 M_r$ and $29–35\times10^3 M_r$ galaptins appear to be multifunctional proteins, demonstrating physiologically important activities in the nucleus, in the cytoplasm, at the cell surface and in the extracellular matrix. It seems that post-translational modifications play important roles in regulating these different activities. The cell surface and extracellular activities of galaptins probably involve an as yet uncharacterised route of secretion and it seems certain that carbohydrate recognition is important in both binding interactions and modulatory processes throughout the cell and its extracellular matrix.

The cellular interactions involved in growth and development involve many complex activities. It is clear that multiple discrete but interactive systems regulate these crucial processes. Unfortunately, the 'cost effective' use of a particular domain structure in different proteins and the evolution of multiple systems with overlapping roles has combined in galaptins to make the investigator's task particularly difficult and prone to confusion. Now the fog is clearing, and it is obvious that investigating these 'molecules in search of a function' is providing revealing insight into generally applicable concepts of cell biology. There are many lines of experimental investigation opening up for exploitation. In the search for their functions, the end may not be in sight but, at last, it is conceivably around the corner.

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