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Cell adhesion and morphogenesis: The regulator hypothesis

(cell adhesion molecules/morphogenetic movements/embryonic induction/regulatory genes/cell surface modulation)

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ABSTRACT **A sequence for the genetic and molecular regulation of morphogenesis is proposed in terms of the regulator hypothesis which is intended to provide a specific molecular framework relating developmental genetics to evolution. The hypothesis derives from an analysis of the interactive morphogenetic roles of the primary processes of cell adhesion, cell movement, and embryonic induction during regulative development. According to the regulator hypothesis, the genes for cell adhesion molecules (CAMs) are expressed in schedules that are prior to and largely independent of those for cytodifferentiation. The expressed CAMs act as regulators of the overall patterns of those morphogenetic movements that are essential for inductive sequences or early milieu-dependent differentiations. It is proposed that, during evolution, natural selection eliminates those organisms in which variants of CAM gene expression or of morphogenetic movements or of both result in interruptions in the inductive sequence. Under this assumption, more than one (but not all) combinations of these two variables will lead to stabilization of the order of inductive sequences and of the body plan in a variety of species. Moreover, small variations in the pattern of action of regulatory genes for CAMs in those organisms that are not selected against could lead to large changes in animal form within relatively short periods of evolutionary time. The experimental bases for the regulator hypothesis are reviewed here in terms of the molecular properties of CAMs and their known spatiotemporal sequences of expression during early embryogenesis.**

How can a one-dimensional genetic code specify the development of the three-dimensional shape of animals? This unanswered question points up morphogenesis as one of the great unsolved riddles in modern biology. In morphogenesis, evolutionary and developmental strategies are intimately entwined by mechanisms of gene action that are extraordinarily complex. Indeed, several different patterns of evolutionary biochemistry must be traced to understand the origin of various animal forms. Development in many protostomes is, for example, largely (but not completely) mosaic, with early determination of blastomeres resulting from the segregation of cytoplasmic components. While mosaicism also occurs in deuterostomes, their development occurs mainly as a result of regulatory interactions between cells of different histories.

During regulative development, morphogenetic movements bring the appropriate cells together in a complex, continuous set of transactions involving both cell contact and molecular signals (1). The interactions of these cells at particular times and positions lead to milieu-dependent differentiations or embryonic inductions and eventually to the establishment of form and of cytodifferentiation within particular organs. Embryologists summarize the significance of cell position in this four-dimensional morphogenetic process by a series of two-dimensional fate maps prepared at successive times. These are maps in which the cells at each particular location in some early embryonic structure (such as the chicken blastoderm) are identified in terms of the particular later structures to which they will give rise within some defined time period. The pivotal issue in understanding the basis of such maps rests in identifying alterations of the timing and mode of action of regulatory genes (2). How can we identify such genes and relate their actions to morphogenesis?

There appear to be two major strategies. The first, particularly applicable to organisms such as *Drosophila*, is to dissect away the gene control systems for morphogenesis from those concerned with cell differentiation. This has been done with increasing success in the case of homoeotic mutations (3, 4). The results point to the existence of cascaded sequences of gene action that can alter the programs by which cells interact to give appendages, segments, and other complex structures. The second strategy is based on another criterion: find a structural gene product with a direct function in morphogenesis, the expression of which is largely independent of organ-specific schedules of cytodifferentiation; having found such a gene product, search for appropriate regulatory genes that control its developmental expression.

It is this strategy that recommends itself in considering vertebrate development in which the genetics is not as readily available to manipulation. In the vertebrates, the focus must be directly upon the primary processes of development: cell division, differentiation, adhesion, migration, and death (5). As Needham pointed out long ago (6), these processes are dissociable—i.e., they can be studied independently by appropriate experimental paradigms. Recent application of this wisdom to cell adhesion has begun to shed light on morphogenesis by revealing important constraints upon the other primary processes exerted by this form of cell interaction. Cell–cell adhesion is the primary process most obviously related to the maintenance of final form and is most directly susceptible to chemical assault. How well do the molecules mediating this adhesion fit the criterion developed in the second strategy for analyzing morphogenesis?

Cell Adhesion Molecules

Cell adhesion molecules (CAMs) of different specificity have now been isolated and characterized in part (7–14). Two different glycoproteins, N-CAM and L-CAM, appear in a specific set of patterns during early embryogenesis, are used subsequently in organogenesis, and remain in adult tissues in distinct patterns that are related to their early distributions. Furthermore, N-CAM has been found in various vertebrate species (15, 16), as has L-CAM (11, 12). Their chemical properties and the nature of their tissue distribu-

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Abbreviations: CAM, cell adhesion molecule; N-CAM, neural CAM; L-CAM, liver CAM; Ng-CAM, neuron–glia CAM; E and A, embryonic and adult forms of N-CAM.

tions suggest a key role for CAMs in morphogenesis. Detailed definition of that role depends upon a knowledge of the relationship between their structure and function.

The largest polypeptide chain of N-CAM is a species of molecular weight 160,000 at all ages, but the molecule also contains a large amount of sialic acid linked as polysialic acid, which changes in amount as a function of age. Because of the presence of this carbohydrate, N-CAM in its embryonic (E) form is microheterogeneous and its apparent molecular weight is 200,000–250,000; this form is converted during later development to two or three adult (A) forms with lesser (but still significant) amounts of sialic acid that migrate on $NaDodSO_4$/PAGE as sharp bands of 180, 140, and 120 kilodaltons (17). This age-dependent process, called E-to-A conversion, has been shown to be related to a significant change in binding behavior. N-CAM on one cell binds to N-CAM on another (homophilic binding) in a calcium-independent manner via a region in the NH_2-terminal domain. The sialic acid is attached in a middle domain and the COOH-terminal domain is most likely inserted in the plasma membrane (18). Kinetic studies of the homophilic binding of N-CAM in membrane vesicles show that E-to-E binding is about 1/4th as rapid as A-to-A binding, with E-to-A binding intermediate in rate (19). Although the sialic acid is not directly involved in binding, it modulates the binding probably as a result of charge effects (9).

In contrast, L-CAM is a "normal" glycoprotein with a different polypeptide backbone than N-CAM and its binding (which has not yet conclusively been shown to be homophilic) depends strongly upon calcium (11). Indeed, in the absence of this ion, L-CAM is rapidly degraded by proteases and presumably the maintenance of its active and stable conformation depends upon Ca^{2+} binding. N-CAM and L-CAM do not bind to each other.

Embryological Behavior of CAMs

Both N-CAM and L-CAM are visualizable in very early chicken embryos by fluorescently labeled antibodies, and their staining appears to be coincident in the early blastoderm of the chicken. During gastrulation and neural induction, however, a very large increase of N-CAM staining and loss of L-CAM staining occur in the region corresponding to the neural plate; a conjugate L-CAM increase and N-CAM decrease take place in surrounding regions (20, 21). An epochal map of these and subsequent distributions of the two CAMs can be constructed by following the staining for each CAM through the completion of organogenesis as seen in the derivatives of the cells that define the classical embryonic fate map, and then noting the regions of the map occupied by the CAMs.

The classical map (Fig. 1*A*) of the chicken embryo is based on the work of Vakaet. Such maps summarize what will become of cells in each embryonic region in terms of their location and collective shape and the structures they will give rise to for a defined period of time or epoch. This results in a map that emphasizes topological features—i.e., exact details of the structures that will emerge are sacrificed to reveal connectedness of regions and neighboring relationships of cells deriving from the blastoderm. It is these relationships that are important in induction events.

The composite CAM fate map (20) shows several striking and significant features (Fig. 1*B*): (*i*) presumptive regions that will display only N-CAM (neural plate, notochord, somites, and some lateral plate mesodermal derivatives such as the heart) are surrounded contiguously by the presumptive regions (nonneural ectodermal and endodermal derivatives) that will contain L-CAM exclusively. The domains occupied by the two different CAMs are each continuous and simply connected. As indicated above, this topological arrangement arose in a sharp transition from a simpler one in which a single domain originally contained both CAMs. (*ii*) There is a coarse cephalo–caudal diminishing gradient of N-CAM distribution that is nonuniform. In the more caudal regions this distribution is dynamic or time dependent: while the cephalic region that will develop into neural tissue contains N-CAM throughout the chicken's lifetime, in contrast, the notochord first has no N-CAM, then the molecule is expressed, and finally it disappears after neurulation. Similarly, somites show a dynamic pattern of N-CAM appearance just at segmentation (20). (*iii*) N-CAM and L-CAM appear in all regions of primary and secondary induction. Each appears in derivatives of more than one germ layer and its expression is therefore not inexorably tied to schedules of cytodifferentiation. This is shown additionally by the fact that the distribution of a given CAM can overlap several boundaries of the classical map even within one germ layer. After its segregation from N-CAM in primary induction, L-CAM is particularly prevalent in gut regions giving rise to organ rudiments and in regions of fusion with ectoderm such as the pharynx. The L-CAM and N-CAM sequence in the kidney is highly dynamic and coordinate: L-CAM is seen in the inductor tis-

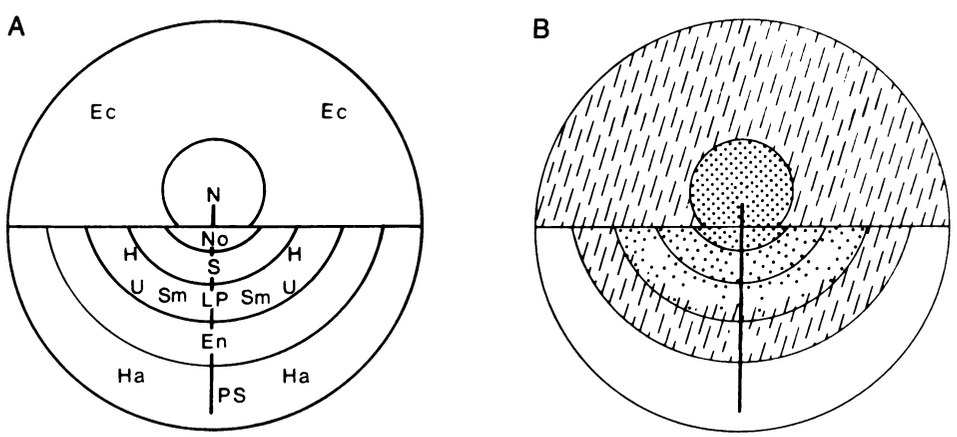

FIG. 1. Composite CAM fate map in the chicken. (*A*) Fate map of the blastoderm, showing areas of cells that will give rise to differentiated tissues. (*B*) Map of cells that will express CAMs. The distribution of N-CAM (stippled) or L-CAM (slashed) on tissues at 5–14 days (stages 26–40) as determined by immunofluorescence staining is mapped back onto the blastoderm fate map. Cells that will give rise to the urinary tract (U) express both L-CAM and N-CAM. Smooth muscle (Sm) and hemangioblastic (Ha) tissues express neither N-CAM nor L-CAM, and areas giving rise to these tissues are blank on this map. The vertical bar represents the primitive streak (PS); Ec, intraembryonic and extraembryonic ectoderm; En, endoderm; H, heart; LP, lateral plate (splanchno- and somatopleural mesoderm); N, nervous system; No, prechordal and chordamesoderm; S, somite. (Data derived from ref. 20.)

sue or Wolffian duct; N-CAM subsequently appears in mesonephric mesenchyme as it organizes into tubules and N-CAM is then replaced by L-CAM as the tubules extend. (*iv*) Some regions, such as hemangioblastic areas (Ha), are blank, suggesting that new CAMs may be discovered in the map. (*v*) Whenever cells detach from tissue masses in epithelia and undergo large movements, detectable CAMs disappear from their surface. Examples are the middle layer (mesoblast) cells during the formation of germ layers, and neural crest cells during their migration. In the case of crest cells, N-CAM reappears at the time of ganglion formation (20, 21).

Epithelial-to-mesenchymal transitions, which are fundamental in early embryogenesis, thus appear to be correlated with an alteration in the amount of CAMs at the cell surface. Indeed, all of the events described above represent changes in prevalence of CAMs, a form of local cell surface modulation (9). In vesicle binding experiments, it has been shown that a 2-fold change in the surface concentration of N-CAM leads to a greater than 30-fold change in rate of homophilic binding (19). The implication is that cell surface modulation of the amount of a CAM during embryogenesis would be expected to have striking effects on binding, movement, and ultimately upon form.

Members of the primary set of CAMs (i.e., those expressed in very early embryos) are used subsequently for key roles in organogenesis: N-CAM for brain and for interaction of neurons with precursors of striated muscle, and L-CAM for liver, gut, pancreas, and various endodermal derivatives as well as for skin (22). In addition to surface modulation in prevalence, N-CAM shows an intrinsic chemical modulation during the perinatal period, the E-to-A conversion, the chemistry of which has already been discussed above. This diminution in sialic acid content increases the rate of homophilic binding (19). It is particularly significant that E-to-A conversion occurs on different schedules in different parts of the brain. Conversion appears to be the result of alterations in enzymatic action of either sialidases or glycosyltransferases and is under genetic control. In view of differences in the binding efficacies of the molecules in different forms (19), aberrations in the conversion from E and A forms would be expected to change connectional patterns that depend upon modulation of adhesion. In accord with this expectation, in mice homozygous for the autosomal recessive staggerer mutation that display cerebellar connectional defects, E-to-A conversion of N-CAM is greatly delayed in the cerebellum at just the times during which there is expression of disordered connections (23). This finding suggests that epigenetic modulation by E-to-A conversion may play an important role in normal brain histogenesis, presumably by selectively increasing the binding efficacy of N-CAM. This would lead to regulation of other morphogenetic primary processes such as migration and nerve process attachment and withdrawal, and possibly even later processes such as synaptic stabilization.

The Regulator Hypothesis

The fate map and the data on early embryogenesis and later histogenesis are compatible with a dynamic model in which differential CAM gene expression occurs in a pattern the topology of which is genetically determined and evolutionarily conserved as part of the body plan. The sequential expression of a small number of different CAM genes in a dynamic pattern would lead to irreversible associations of certain cells, folded sheets of cells, and cell masses; further differentiation events would then be expressed and conditioned by the inductive signals that ensue.

The dynamic events as presently understood are schematized in a temporal diagram (Fig. 2), which shows N-CAM and L-CAM (1° set) appearing first together, with divergence

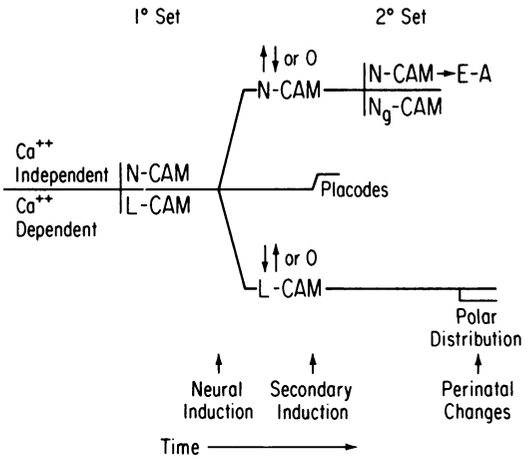

FIG. 2. Temporal sequence of expression of the known CAMs. The diagrammed events are based mainly on work in the chicken. N-CAM and L-CAM are first expressed together but then diverge in cellular distribution (see Fig. 1) at neural induction. They are then modulated in prevalence (⇅) within various regions of inductions or they actually disappear (0) at the cell surface when mesenchyme is formed or cell migration occurs. Placodes, which initially have both CAMs, echo the events seen for neural induction. Just before appearance of glia in the central nervous system, a secondary-set CAM (Ng-CAM) emerges. In the perinatal period, a series of epigenetic modulations occurs: E-to-A conversion for N-CAM and polar redistribution for L-CAM. The regulator hypothesis states that activation of a set of regulatory genes controlling a small number of CAM structural genes leads to the expression of a particular CAM at the cell surface and the suppression of other CAMs. This alters cell–cell adhesion and therefore regulates morphogenetic cell movements. The patterns of movement and adhesion in turn control embryonic induction as well as activation of other regulatory genes, particularly those concerned with cytodifferentiation. Regulation of CAM genes is thus considered to be prior to and relatively independent of cytodifferentiation schedules until later stages in which histogenesis occurs.

of their spatial distribution at neural induction, and subsequent increases, decreases, or disappearances (⇅ or 0) occurring for the CAMs that are characteristic of each tissue. Placodes echo the differential CAM expression; both CAMs are initially present but subsequently, in placodes destined for neural structures, L-CAM disappears and N-CAM increases. Genes for Ng-CAM (a 2° set molecule which binds neurons to glia) are expressed later (24), leading to the appearance of this molecule on neurons. The fact that this second neuronal CAM is not expressed during early embryogenesis but only at 3½ days in the chicken embryo just before the appearance of glial cells suggests that temporal control of CAM gene expression is also critical in histogenesis. A reasonable interpretation is that CAM genes for secondary set molecules, such as those for Ng-CAM, would be called into play sequentially to provide for more complex cellular interactions that are necessary during differentiation of certain organs. Later, in the perinatal period, E-to-A conversion occurs in N-CAM while polar redistributions of L-CAM occur on cells of certain tissues such as those of the pancreas. Epigenetic alteration arising from E-to-A conversion of certain CAMs and initiated by enzymes that are themselves under control of additional regulatory genes would provide further components of selectivity to the dynamic picture of primary set CAM gene expression, particularly during organogenesis.

We are now in a position to construct a hypothesis on the molecular regulation of morphogenesis and thus address the question of how the form of a three-dimensional animal can arise from a one-dimensional genetic code. The pivotal point of the hypothesis is that CAMs at the cell surface act either

directly or indirectly as regulators or steersmen for the other primary processes. It is reasonable to propose that the genes regulating the expression of CAM genes are a special set controlled by mechanisms independent from those regulating cytodifferentiation; this appears to be reflected in the fact that a CAM in the composite map (Fig. 1) is expressed early and remains in structures that span classical map boundaries not only within a germ layer (somites, heart, kidney) but also across germ layers (all three for L-CAM; ectoderm and mesoderm for N-CAM). CAM expression must play a direct role in the control of motion that is the result of the play between cellular motility, tension in tissue sheets, and adhesion.

Whether a cell moves is a balance between its inherent motility and the alternative opportunities provided by cell–cell adhesion mediated by CAMs and by cell–substrate adhesion mediated by substrate adhesion molecules (SAMs). This is seen particularly well in the case of neural crest cells (20, 21), which lose surface N-CAM during movement on fibronectin layers. It is such morphogenetic movements that bring cells and tissues of different history together in the embryonic inductions that will determine succeeding steps of the morphogenetic process. It should be noted, however, that while the role of CAMs as regulators of movement and thus indirectly of induction has experimental support, the direct role (if any) of CAMs in induction remains to be worked out, as do most of the mechanisms connecting CAM binding to those cellular responses that are related to primary processes other than adhesion and migration.

Although the factors that trigger the regulatory genes for CAMs are not known, when they are triggered, a series of CAM expressions and surface modulations (9) of the expressed CAMs occurs that sharply constrains other cellular possibilities. Because embryonic processes are historical, even the same repeated sequence of expression of N-CAM and L-CAM genes (see Fig. 2) would give rise dynamically to new structures in successive and different cellular contexts. These contexts can only arise, however, if they are preceded by previous inductive sequences in the appropriate order.

According to this picture, it is possible to understand why different vertebrates might have different gastrulation patterns, morphogenetic movements, and details in their fate maps and yet share a basic body plan. Natural selection during evolution would allow only those organisms to survive in which individual particular combinations of variant morphogenetic movements and variant CAM gene expressions led to the appropriate functional inductive sequences. But more than one such combination could occur, and successful combinations of movement patterns and gene expressions which are quite variant from species to species could yield similar inductive sequences. If this aspect of the regulator hypothesis were true, large morphological variations would be possible in short evolutionary times because of the enormous effects upon morphogenesis of even small permitted changes in CAM regulatory genes.

This analysis suggests a plausible way by which the critical early determinants of form could arise from certain embryonic molecular processes: structural genes for a few CAMs of different specificity are expressed according to an evolutionarily stabilized topological plan and under temporal control of regulatory genes that are largely independent of those involved in later cytodifferentiation.

A number of predictions flow from the regulator hypothesis:

(*i*) The number of primary set CAMs will be small (but not necessarily limited to N-CAM and L-CAM). This set will be shared by a broad range of vertebrate species as well as the more immediate descendents of protochordates. In the case of certain molecules, such as N-CAM, structurally related precursors may be found in invertebrates; this is particularly likely to be so in animals with nervous systems because of the relatively ancient character of neural cells.

(*ii*) Additional (or secondary set) CAMs will be found that correlate with the occurrence of later histogenetic events but are not expressed in very early embryos. There is a high probability that such CAMs will be found to share common evolutionary precursors with primary set CAMs; indeed, they may exist as a small gene family. Despite the existence of secondary set CAMs, those in the primary set will continue to play key roles at all later stages of organogenesis and regeneration.

(*iii*) Regulatory genes for CAM expression will be controlled by mechanisms independent from those involved in the expression of products of cytodifferentiation within specific tissues. It would not be surprising if some of the genes responsible for homoeotic mutants regulated the expression of a series of CAM-like molecules.

(*iv*) The spatial expression of a small number of primary set CAMs in early fate maps will be topologically similar in a variety of animal species showing the same body plan despite the great variation in their early morphogenetic movements, gastrulation schedules, and fate map details. To make the prediction specific, the frog will, for example, have a composite CAM map that is topologically similar to that of the chicken (see Fig. 1) even though the morphogenetic movements and topographic details leading to the fate maps in these two species are quite different. The topology is expected to be the same in various species with similar body plans because similar inductive sequences within and between different germ layers would in all likelihood require similar borders between different CAMs. This topological requirement would be strongest at earliest times (for example, in primary induction) and it would also be expected to hold inexorably for the distribution among particular germ layers of a given kind of CAM. Occasional deviations, if they occur at all, would be expected only at later times of organogenesis, when most inductions have already occurred.

The regulator hypothesis would have to be abandoned if any of the first, third, or fourth of these predictions is not fulfilled. Even if the hypothesis is confirmed, it remains an open question whether the action of CAM regulatory genes is triggered by morphogens or is triggered by feedback from CAM interactions and spatial asymmetries: while the hypothesis sharpens this fundamental question ("Quis custodiet ipsos custodes?"), it does not supply an answer to it.

Summary

It may be useful to summarize the regulator hypothesis in order to emphasize that it is intended to provide a molecular framework relating developmental genetics to morphogenesis and evolution. The hypothesis can be succinctly expressed in six statements:

(*i*) Cell adhesion molecules (CAMs) play a central role in morphogenesis by acting through adhesion as steersmen or regulators for other primary processes, particularly morphogenetic movements. CAMs exercise their role as regulators by means of local cell surface modulation (9). (*ii*) Genes for CAMs are expressed in schedules that are prior to and relatively independent of those for particular networks of cytodifferentiation in different organs. (*iii*) The control of CAM structural genes by regulatory genes is responsible for the body plan as seen in fate maps. In the chicken, this plan is reflected in a topological order: a simply connected central region of N-CAM surrounded by a contiguous simply connected ring of cells expressing L-CAM. (*iv*) Morphogenetic movements are resultants of the inherent motility of cells and of CAM expression as it is coordinated with the presence of substrate adhesion molecules (SAMs) and substrates such as fibronectin (9, 21). These movements, which are reg-

ulated by CAM modulation, are responsible for bringing cells of different history together to result in various embryonic inductions. (*v*) Natural selection acts to eliminate inappropriate movements by selecting against organisms that express CAM genes in sequences leading to failure of induction. On the other hand, any variant combination of movements and timing of CAM gene expression (resulting from variation in regulatory genes) that leads to appropriate inductive sequences will in general be evolutionarily selected. This allows for great variation in the details of fate maps from species to species but at the same time tends to conserve the basic body plan. (*vi*) Small changes in CAM regulatory genes that do not abrogate this principle of selection could nevertheless lead to large changes in form in relatively short evolutionary times.

Finally, it is perhaps important to note that this model is parsimonious in respect to the total number of genes involved. Because of the wide dynamic range of cell surface modulation effects (9, 19) and their temporal permutations (23), the developmental and evolutionary effects of the variant expression of a rather small number of genes related to cell adhesion could be momentous. Further experiments are required to clarify this picture but, in the view so far, the analysis of adhesion promises to provide a reference for the study of the other primary processes that are essential to morphogenesis. While these primary processes would provide the key morphogenetic driving forces, the temporally regulated expression of CAM genes would provide a large part of the selectivity that guides and kinetically constrains the interaction of these processes during the generation of form.

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