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REVIEW PAPERS

CELL ADHESION MOLECULES IN TERMS OF CARCINOGENESIS

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Cell adhesion molecules (CAMs), or adhesins, are glycoproteins being components of the cell membrane. They are involved in the cell–cell, and cell–extracellular matrix interactions. As being present in tight junctions and adherens junctions in tissues, they determine the integrity and properties thereof. They also function as receptor proteins through modulating transduction of information to the interior of the cell in a form of a signal triggering the activation of appropriate cascades of chemical reactions, with the consequence of a specific response thereof. Therefore, a change in CAM gene expression will result in different cell behaviour and properties of the tissue (1, 2). The characteristics as described above explain the role of CAMs in wound healing, immunological processes, leukocyte diapedesis, inflammation processes and, finally, carcinogenesis and metastasis. They also modulate such intracellular processes as cell differentiation, proliferation and apoptosis (2).

1. GENERAL STRUCTURE AND DIVISION OF CELL ADHESION MOLECULES

CAMs are comprised of amino acid chains linked with disulfide bonds. 3 components of CAMs are distinguished: cytoplasmic domain coupled to the cytoskeleton, transmembrane domain being characteristic of receptor proteins, and extramembrane domain which determines the contact with the external environment, and binds to either a domain of another adhesin or the extracellular matrix (ECM). The structure being described mainly concerns the transmembrane form of cell adhesion molecules (membrane CAMs, mCAMs); a group of cell adhesion molecules being soluble in body fluids (soluble CAMs, sCAMs) is also distinguished (2). According to the generally accepted division, the following CAM groups are distinguished: immunoglobulin superfamily cell adhesion molecules, integrins, selectins, CD44 proteins, and cadherins. It should be noted that there is no single, consistent classification of cell adhesion molecules, since CAMs originate from numerous groups being different in both the structure and properties; however, they are linked by a similar function (1, 2, 3).

2. IMMUNOGLOBULIN SUPERFAMILY CELL ADHESION MOLECULES (IgCAMs).

This group is comprised of transmembrane glycoproteins characterized by the extramembrane domain being analogous to immunoglobulin. The group includes CAMs involved in the immunological processes of signal transduction (CSF1 and PDGF receptors), and in processes responsible for cell integrity (neuronal CAMs (NCAMs), vascular cell adhesion molecules (VCAMs), CD106, intercellular adhesion molecules (ICAMs), platelet endothelial cell adhesion molecules (PECAMs), mucosal vascular addressin cell adhesion molecule

(MAdCAM), as well as the carcinoembryonic antigen (CEA) (2). IgCAMs are capable of forming complexes with each other (e.g. two NCAMs) and with other molecules (3). With the downregulation or loss of expression of IgCAMs on lymphocytes, their functions of recognizing and eliminating neoplastic cells are disrupted (4).

2.1. INTERCELLULAR ADHESION MOLECULES (ICAMs). These are expressed on leucocytes, mainly on T and B lymphocytes, monocytes, and eosinophils, but also on dendritic cells, fibroblasts, and hepatocytes (fig. 1). ICAM expression is increased under the influence of inflammatory mediators such as IL-1, TNF-α, and LPS (2). Three forms of ICAMs are described: ICAM-1, ICAM-2 and ICAM-3 (5). Physiologically, ICAM-1 is expressed on endothelial and epithelial cells, as well as on pneumocytes where it is essential for immunological functions, proliferation, differentiation and motility of cells. Molecules of the ICAM group also perform a role in the processes characteristic of inflammatory conditions of the body (6). Increased expression of this isoform also plays a role in the pathogenesis of a number of neoplasms such as colorectal cancer, gastric cancer and breast carcinoma. In this case, the increased expression may be associated with a better prognosis, which is a base for suspecting an improvement of the function of the body's immune system. Furthermore, it may accompany the increased aggressiveness of such neoplasms as malignant melanoma, pulmonary carcinoma and pancreatic cancer, but also gastric and breast carcinoma, which proves the complexity of the signalling processes of cell adhesion molecules (7).

2.2. VASCULAR CELL ADHESION MOLECULES (VCAMs). The presence of those molecules has so far been observed on endothelial cells, lymphocytes, monocytes and macrophages, eosinophils and dendritic cells; they are also expressed on neoplastic tumour cells. Their expression is increased under the influence of IL-1, IL-4, IL-13, and TNF-α and LPS. (2). VCAM-1 is a classic example of a cell adhesion molecule of the immunoglobulin superfamily of cell adhesion molecules (fig. 2). It may be present in a form bound with the cell membrane, but also in a soluble one, determined in the serum (sVCAM-1). It plays a role in functioning of the bone marrow and lymphatic system, conditions of the cardiovascular system, and, as previously mentioned, in inflammatory processes and neoplasms (8). In the latter case, the mechanism of action is supposed to involve blocking the migration of T lymphocytes to the tumour environment, thus decreasing the efficiency of the action thereof and slowing down the progression of the neoplasm. Indeed, in immunohistochemical tests, the absence of or a decreased expression of this VCAM-1, along with ICAM-1, was observed on the unchanged intestinal epithelium cells, as opposed to the well-differentiated adenocarcinoma cells where the expression was significantly higher. Similar observations were made

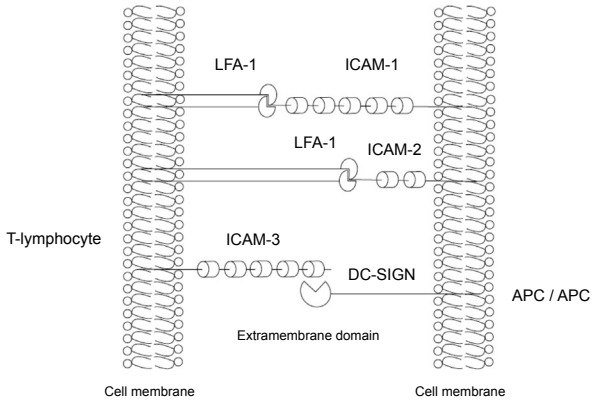

Fig. 1. Interactions of intercellular adhesion molecules (ICAMs) between a lymphocyte and an antigen presenting cell (APC) (an original drawing)

ICAM-1,2,3 – isoforms of the intercellular adhesion molecule (ICAM). LFA-1 – integrin. APC – Antigen Presenting Cell.DC-SIGN – Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin

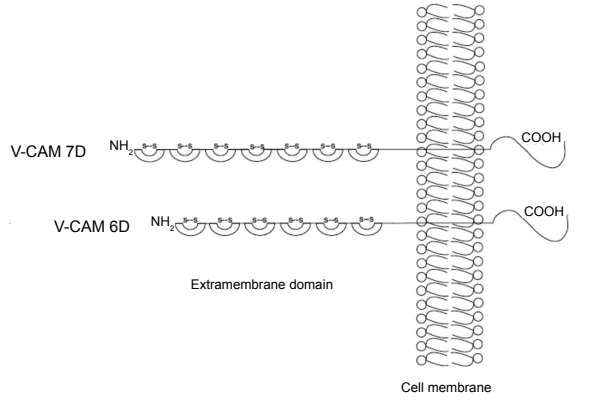

Fig. 2. Isoforms of VCAM proteins

The figure presents two isoforms of V-CAM proteins, containing 6 and 7 immunoglobulin-like molecules in extramembrane domains

for metastases of digestive system tumours to the liver (1).

2.3. PLATELET ENDOTHELIAL CELL ADHESION MOLECULES (PECAMs). Large amounts of this protein have been determined on the junctions between endothelial cells, platelets and white blood cells (monocytes, neutrophils, and certain T lymphocytes) (2). PECAM-1 (fig. 3) plays an important role in the inflammatory processes; the expression thereof on leucocytes allows them to penetrate the blood vessel cell. Studies confirming the link between angiogenesis in the adjacent tissue with the development of colorectal cancer indicated an increased PECAM-1 expression along with the differentiation, severity and the size of the tumour. It has also changed depending on the presence of metastases to the lymphatic nodes (9). PECAM-1 is therefore associated with worse prognoses for a number of neoplastic tumours, also in gastric lymphoma where it may be considered to be an independent prognostic factor (10).

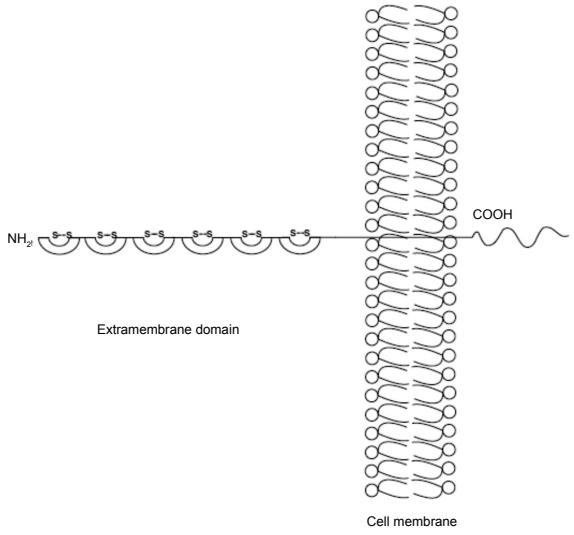

Fig. 3. PECAM cell adhesion molecule (an original drawing)

The figure presents PECAM cell adhesion molecule belonging to the immunoglobulin superfamily of cell adhesion molecules. The extramembrane domain is comprised of 7 immunoglobulin-like molecules

2.4. MUCOSAL VASCULAR ADDRESSIN CELL ADHESION MOLECULE (MAdCAM)

MAdCAM-1 is a protein primarily found of the so-called high endothelial venule-like vessels (11, 12). The author of the paper has failed to find studies in the literature, which had undertaken to directly link the expression of this protein genes with the development and characteristics of the CRC. On the other hand, numerous authors have been undertaking to carry out studies on the involvement of those molecules in inflammatory diseases, including the Inflammatory Large Bowel Diseases (13), which allows one to suspect, at least indirectly, the involvement of the molecules concerned in the carcinogenesis of CRC.

2.5. CARCINOEMBRYONIC ANTIGEN (CEA). This is one of the most recognized cell adhesion molecules, being used for the diagnosis of CRC. CEA is expressed on both the CRC cells and on the normal large intestinal crypts. Its expression is also observed in the case of pulmonary carcinoma where it also has a clinical use as a tumour marker, as well as in the cases of other neoplasms. It has neither transmembrane domain or cytoplasmic domain (fig. 4), and is expressed both intracellularly and extracellularly (1). It is found in both a free form circulating in the serum, and in a bonded form being capable of binding with own molecules, and with other cell adhesion molecules. It is believed that CEA triggers the release of IL-1, IL-6 and TNF-α which, while stimulating ICAM expression, facilitate the migration and adhesion of neoplastic cells, and, as a result, the formation of metastases of CRC in the liver (13).

3. INTEGRINS Those proteins are expressed on epithelial and endothelial cells. They co-create focal adhesion plaques in the intercellular junctions, and bind extracellu-

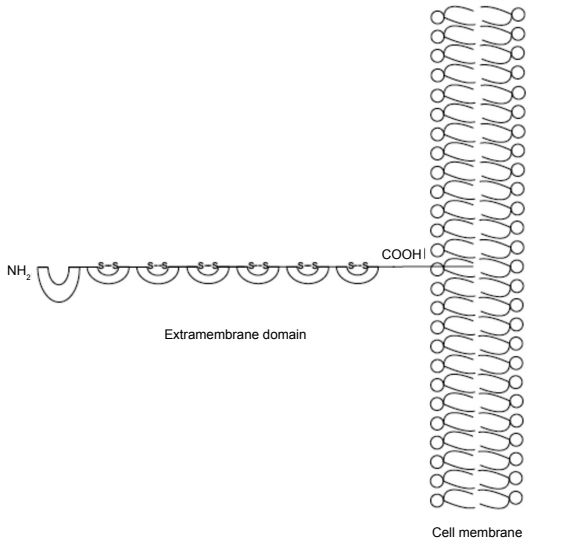

Fig. 4. Carcinoembryonic antigen (CEA) (an original drawing)

Carcinoembryonic antigen as a specific form of a cell adhesion molecule

larly with ECM and, intracellularly, with the cellular cytoskeleton – directly, or with the participation of other proteins (fig. 5). Their activation is triggered by interactions with cytokines, hormones, growth factors or other cells. Similarly to other cell adhesion molecules, integrins are crucial in maintaining tissue integrity, cell migration and apoptosis, the regulation of the cell growth cycle, and, primarily, in the signal transduction (1). Changes in the integrin expression patterns have been observed in a number of neoplasms such as mammary cancer, prostate cancer, colon cancer, and melanoma. Those changes are also supposed to be of significance in the formation of metastatic tumours. In this case, integrins may be involved in the interactions between the basement membrane and the extracellular matrix through the activation of a proteolytic cascade. Furthermore, certain forms of integrins may bind with laminin, forming signaling complexes triggering the oncogenic receptors of a type of tyrosine kinase transduction, such as HER2, Met, and EGFR (5). This explains the phenomenon of the inhibition of the progression of development of colorectal cancer, and the inhibition of the formation of metastases thereof, through blocking the degradation of the extracellular matrix. Moreover, the inhibition of alphavbeta3 and alphavbeta5 integrins in tissue preparations of the metastasis of colorectal cancer to the liver results in a significant reduction in cell proliferation on collagen base, which demonstrates the crucial role of those proteins in the formation of metastases. They are also important in the formation of junctions between the tumour and endothelial cells, supporting the angiogenesis of the area surrounding the lesion site. What is interesting in this aspect is the findings as formulated by van der Voort van Zijp et al. (14), who provided a report on the significance of mechanical pressure during the manipulation on a tumour and the surrounding tissues during the surgical procedure on enhancing the aggressiveness of neoplastic cells on the base of the loss of tissue integrity. In this case, the mechanical pressure is supposed to enhance the adhesive properties of the tumour cells through the impact on its integrins (14). Finally, integrins are a promising target for the biological targeted therapy; they have been attributed a certain significance in a number of neoplasms e.g. gliobliastoma (15) or colorectal cancer (16).

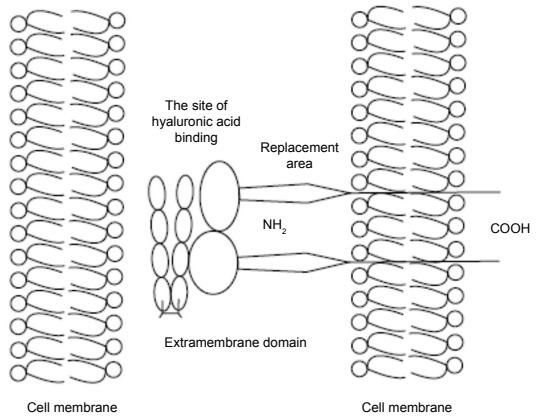

Fig. 5. Integrin (an original drawing)
The figure presents an interaction of two adjacent cells through a cell adhesive molecule of the integrin group

4. SELECTINS Selectins have a structure of glycoproteins in which the N-end has a form of lectin. A function of the lectin domain is to bind glycoproteins of other cells. This fact demonstrates the involvement of those proteins in maintaining the integrity of tissues (fig. 6) (17). Depending on the number of repetitions of sequences similar to the complement system, three selectin classes are distinguished: L-selectin which is found on leukocytes; endothelial E-selectin, and platelet P-selectin. The first of the molecules being described is expressed on leukocytes; however, following their activation, it may be released from their cells and be found in a free form determined in the blood serum. The occurrence of E-selectin has been determined in the endothelium being under the influence of the impact of IL-1 or TNF-α (and thus in the presence of an inflammatory condition). It is syn-

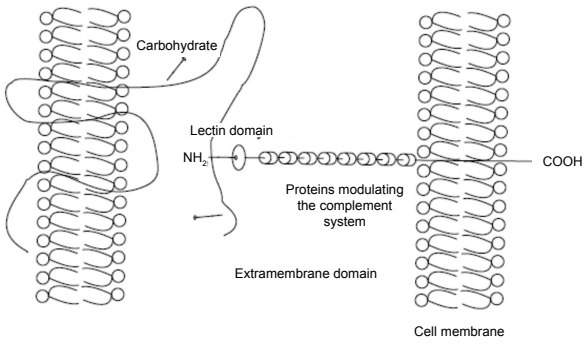

Fig. 6. Selectin (an original drawing)
The figure presents an interaction of two adjacent cells through a cell adhesive molecule of the integrin group

thesized in the endothelial cytoplasm, and transported to the membrane thereof, with the activation of inflammatory leukins. The latter of the proteins in the group being described is P-selectin which is also found in the endothelium (2).

It is believed that an increase in selectin activity indicates a worse prognosis in the event of neoplasms; furthermore, the pathways supposed to promote the development of a neoplasm are linked with those responsible for inflammatory processes, which may explain the overlapping of the processes being described. As mentioned previously, E-selectin is mainly expressed on the endothelial cells; in addition to the described functions, it may bind with neoplastic cells and change the expression of their genes, and thus the biology of the neoplasm. It may also modulate the permeability of the epithelium through the activation of p38 and ERK AP kinases. An increase in the expression of the selectin of this class is associated with the formation of metastases of colorectal cancer to the liver, and the inhibition of this expression under laboratory conditions is supposed to result in the inhibition of the development of metastases to that organ.

The P-selectin class also contributes to carcinogenesis. Platelets, while reacting with the tumour cells as released to the blood stream, support the formation of neoplastic miniemoblisms. It is assumed that the group of P-selectins is responsible for exactly those processes; this relationship has been observed for processes associated with the formation of metastases to the lungs. L-selectin is another class of this group of cell adhesion molecules, the expression of which is related to the promotion of the formation of metastases. It has been found experimentally that the absence of L-selectin leads to the inhibition of the formation of metastases, which is related to the activation of leucocytes and the processes as described above. The above observations naturally predispose this group of cell adhesive molecules to be a potential target for the biological targeted therapy of neoplasms. Not only are appropriate antibodies and glycomimetics mentioned here as therapeutic substances, but also heparin with which clinical studies are being currently carried out (17).

5. CD44 MOLECULES CD44 is involved in maintaining tissue integrity through the participation in interactions between cells, and between cells and ECM. It is involved in the activation of T-lymphocytes, modulates their properties in relation to the endothelial cells, triggers the release of cytokins, and participates in the processes of fibrosis. It is a receptor for hyaluronic acid (2), collagen, laminin, and fibronectin. Changes in the expression thereof have been described for a number of neoplasms such as mammary cancer, prostate cancer, ovarian carcinoma, cervical carcinoma, colorectal cancer and neuroblastoma. Even though for a number of neoplasms, e.g. mammary cancer, an increased CD44 expression has been associated with the progression of the disease, the function of CD44 as a receptor may be associated with both the promotion and the inhibition of carcinogenesis. It should be noted here that it does not have the properties of tyrosine kinasis, and that it exerts the biological effect through recruiting appropriate kinases in the cell cytoplasm, activating the pathways OF GTPase, Ras-MAPK, of PI3K/AKT (18).

6. CADHERINS. Cadherins are among the most recognized cell adhesion molecules, with the functions being analogous to those of the other ones, and a structure similar to three-component glycoproteins. A characteristic feature of cadherins is the dependence of binding of their molecules on the presence of calcium ions. The cadherin family is divided into 3 main classes: neuronal cadherins (NCAMs), endothelial cadherins (ECAMs), and placental cadherins (PCAMs) (22).

6.1. NCAMs. Proteins of this group are mainly found on the neuroendocrine cells, and NK lymphocytes. Expression of this group of cadherins is in inverse proportion to the adhesive properties of the tissue: it is present in the embryonic tissue, disappears in the mature tissue, and re-appears during carcinogenesis of neoplasms such as neuroblastoma, rhabdomyosarcoma, carcinoma of the lung (in this case, it is supposed to promote the detachment of neoplastic cells, allowing the formation of metastases). What is characteristic of NCAMs is the content of polysialic acid (polySia) in the molecule (20); an increase in the content thereof influences the enhancement of adhesive properties of the molecule, and also determines the assignment of this protein to the class with a low content of sialic acid (NCAM-L), and a high content of sialic acid (NCAM-H). NCAM-L groups together three isoforms, de-

pending on the weight of the molecule (fig. 7). Majority of the molecules being discussed contain in their chains immunoglobulin and fibronectin, and they bind with the cytoplasmic membrane with the use of glycosylphosphatidylinositol. NCAM-H, in the embryonic tissue cells, blocks the site of binding thereof with each other, and thus allows the migration. It is assumed that proteins in this group may be involved, in the above context, in the processes of regeneration and signal transduction. They are also physiologically found in the nervous tissue as well as tissues of the small intestine, colon, and testicles (21).

6.2. ECAMs. E-cadherin, as coded by homologous *CDH1* genes, is among the most recognized cadherins (fig. 8). It is directly responsible for the integrity of tissue through the formation of intercellular junctions, mainly in a form of adherens junctions. A reduction in the expression of this protein accompanies the development of most neoplasms, promoting the invasiveness, and conditioning worse differentiation and an enhanced capability of metastasis (22). In addition to the form associated with the cell membrane, there is also a soluble pool of E-cadherins which may be determined in the blood serum. They are supposed to appear there through proteolytic processes in the process of natural regeneration and exchange of this group of proteins, the their physiological concentration is increased in patients with neoplasms (2). An interesting phenomenon is an increased ECAM expression in the tissue of metastatic tumours as compared to the healthy one, especially in the central parts of the lesion. They probably allow the formation of metastases, enhancing the integrity of the neoplastic tissue. A reduced ECAM expression is characteristic of lesions at the epithelial level, accompanying the neoplastic transformations (polyps, adenomas). A similarly reduced cadherin expression has also been described for a number of other neoplasms such as mammary carcinoma, gastric carcinoma, hepatocellular carcinoma, esophageal cancer, and thyroid carcinoma (22).

6.3. PCAMs. Placental cadherin is a glycoprotein coded by the *CDH3* gene (23). Similarly to other cadherins, in is involved in the embryogenesis, being mainly expressed on the trophoblast cells; it is also determined in the stratified squamous epithelium. As opposed to ECAMs, an increase in the PCAM expression

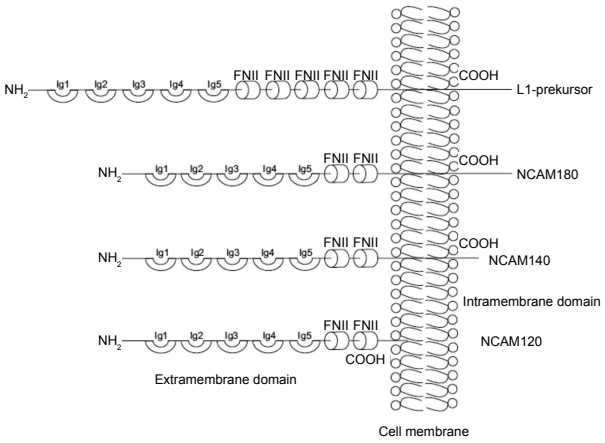

Fig. 7. Isoforms of the neuronal cadherin (NCAM) (an original drawing)

Particular isoforms of the neuronal cadherin, differing in the weight of the molecule

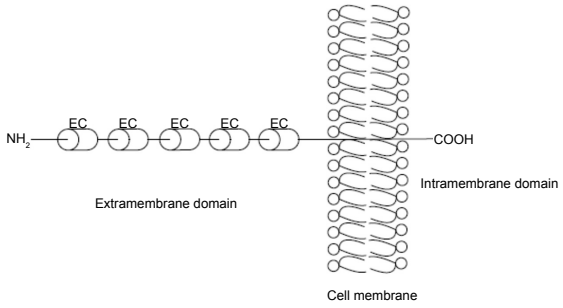

Fig. 8. Epithelial cadherin (ECAM) (an original drawing)

Diagram of the structure of a cell adhesive molecule of the E-cadherin group

level is associated with the progression of malignant neoplasms such as pancreatic cancer, esophageal cancer, bladder cancer, mammary carcinoma and colorectal cancer; an increase in the expression of the latter is supposed to be related to demethylation of the molecule (24), which, so to speak, naturally makes them a potential subject of the immunotherapy of neoplasms (25).

SUMMARY

Cell adhesion molecules play a crucial role in the processes related to the formation and development of a neoplasm, as well as the formation of metastases to other organs. Recognition of their functions and the impact on their expression allows definitely better diagnostics

of a disease and the treatment thereof, which has for a long time been used in the clinical practice. An enormous number of particular groups of cell adhesion molecules, and the complexity of their signaling pathways presents us with a tremendous challenge; however, it also gives us hope for excellent results of the treatment of neoplastic diseases in the future.

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