Induction of Prostaglandin G/H Synthase-2 in a Canine Model of Spontaneous Prostatic Adenocarcinoma

Claudine Tremblay, Monique Doré, Philip N. Bochsler, Jean Sirois

Background: Prostate cancer is the most frequently occurring cancer in men in the United States, with an estimated 179,300 new cases in 1999. The induction of prostaglandin G/H synthase (PGHS), a key rate-limiting enzyme in prostaglandin biosynthesis, has been implicated in various cancers, most notably in colorectal cancers; however, the induction of PGHS expression in prostate cancer in vivo has not been reported for any species. The dog is the only nonhuman species that frequently develops spontaneous cancer of the prostate with increasing age, and the objective of this study was to determine whether PGHS isoenzymes were expressed in canine prostatic adenocarcinomas. Methods: Four normal canine prostatic tissues and 24 canine prostatic adenocarcinomas were studied by means of immunohistochemistry and immunoblot analysis, using polyclonal antibodies specific for each of the two PGHS isoenzymes, PGHS-1 and PGHS-2. All P values were obtained by use of two-sided Fisher's exact tests. Results: PGHS-1 immunostaining was localized to stromal fibroblasts and vascular endothelium in normal and cancerous prostates. PGHS-2 was not detected in normal prostates, but it was expressed by epithelial tumor cells in 18 (75%) of the 24 adenocarcinomas (P = .01). Immunoblot analysis confirmed the presence of PGHS-1 (69,000 molecular weight) in normal and cancerous tissues and the expression of PGHS-2 (72,000- to 74,000-molecular-weight doublet) only in prostatic adenocarcinomas. Conclusion: To our knowledge, these results demonstrate for the first time that PGHS-2 is induced in the majority of canine spontaneous prostatic adenocarcinomas and suggest that its expression may be involved in prostate cancer. [J Natl Cancer Inst 1999;91:1398–1403]

Prostate cancer is the most frequent cancer of men in the United States, with an estimated 179,300 new cases in 1999 [1]. The dog represents the only nonhuman species that frequently develops spontaneous cancer of the prostate with increasing age [2]. Several aspects of canine prostate cancer are similar to the human disease, and the relevance of the dog as an animal model to study prostatic carcinogenesis was recently highlighted [3]. In both species, adenocarcinoma of the prostate affects older subjects and is a locally invasive and insidious disease that metastasizes to distant tissues [3,4]. Also, prostatic intraepithelial neoplasia, the most likely precursor of some human prostate cancers, occurs spontaneously in the prostate of elderly, sexually intact dogs, and the majority of dogs with prostate cancer present high-grade prostatic intraepithelial neoplasia [5–7].

Prostaglandins play a role in the regulation of several important physiologic and pathologic processes, and evidence [8–10] suggest that they could be involved in tumor progression. Prostaglandin G/H synthase (PGHS; also known as cyclooxygenase or COX) is the key rate-limiting enzyme in the biosynthetic pathway of prostaglandins from arachidonic acid [11,12]. Two forms of PGHS have been characterized and are known as PGHS-1 (or COX-1) and PGHS-2 (or COX-2) [13–16]. PGHS-1 is constitutively expressed in various tissues and was originally referred to as the constitutive isoform involved in the synthesis of prostaglandins necessary for normal cellular processes [17,18]. In contrast, PGHS-2 is generally undetectable in most tissues, can be induced by different agonists, and was referred to as the inducible isoform involved in inflammation [17,18]. However, results from PGHS-1 and PGHS-2 gene-targeting studies in mice [19–21] suggest that both isoenzymes participate in physiologic and inflammatory processes.

Mounting evidence [8–10,18] suggests that PGHS-2 plays a role in cancer progression. Increased expression of PGHS-2 has been demonstrated in human colon, lung, and gastric cancers and in esophageal high-risk noncancerous lesions [22–26]. Oshima et al. [27] reported that introduction of a knockout mutation of the PGHS-2 gene in an Apc (adenomatous polyposis coli) knockout mouse (Apc is the mouse homologue of the human APC gene that has been linked to familial adenomatous polyposis) results in a substantial reduction in the number and size of the intestinal polyps. Moreover, the long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), which act on PGHS, appears to have a protective effect on the incidence of colorectal cancer [8–10]. Enhanced expression of PGHS-2 has also been documented following ultraviolet B irradiation of keratinocytes, suggesting its involvement in skin tumor development [28]. A potential role for PGHS-2 in human prostate cancer has been proposed by recent studies in vitro with the use of human prostatic cancer cell lines. Exogenous prostaglandins E2 were shown to increase PGHS-2 transcripts [29], whereas a selective COX-2 inhibitor, NS398 (N-[2 cyclohexyloxy-4-nitrophenyl]methanesulphonamide), induced apoptosis [30]. A recent epidemiologic study [31] reported that the regular use of NSAIDs may reduce the relative risk of prostate cancer. However, the incidence of PGHS expression in spontaneous prostate cancer has not been reported for any species. Therefore, the objectives of this study were to determine whether PGHS isoenzymes are expressed in canine prostate cancer and, if so, to identify which isoenzyme is involved (PGHS-1 and/or PGHS-2) and to determine its cellular localization.

Materials and Methods

Tissue Samples and Platelet Isolation

Twenty-four cases of canine prostatic adenocarcinomas submitted to the Département de Pathologie et Microbiologie of the Faculté de Médecine Vétérinaire (Université de Montréal) and the Department of Pathology of the College of Veterinary Medicine (University of Tennessee) were included in the study. All cases were confirmed as prostatic adenocarcinomas by examination of hematoxylin–eosin–safran-stained sections by a veterinary pathologist.

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See “Notes” following “References.”

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The malignant nature of the prostatic tumors was defined by use of criteria such as anaplasia (anaplo-
cytosis, pleomorphism, anisokaryosis), loss of nor-
mal polarity, anarchic growth, atypical mitotic fig-
ures, and local or vascular invasion. The histologic
classification used was the World Health Organiza-
tion International Histological Classification of Tu-
mors of Domestic Animals (32). Normal prostates
were obtained from four adult dogs (one Rott-
weiler, one Mâtin de Naples, and two mixed breed
dogs; ages between 3 and 6 years) euthanized for
reasons unrelated to health problems. All tissues
were fixed in 10% neutral buffered formalin,
whereas samples from two normal prostates and two
adenocarcinomas were frozen at −70 °C for immu-
noblot analysis.

Canine plateslets were isolated from whole blood
collected by venipuncture from a healthy adult dog
in anticoagulant (citrate phosphate dextrose solu-
ton; Abbott Laboratories, Chicago, IL). Platelet-
rich plasma was isolated by successive centrifuga-
tions at room temperature of the citrated blood for 3
minutes at decreasing speed (700g; 650g, and 600g),
as previously described (33). Platelets were recov-
ered from the platelet-rich plasma by centrifugation
at 16 000g for 10 minutes at room temperature and
were stored at −70 °C. All animal procedures were
approved by the institutional animal care and use
committee of the Université de Montréal.

Anti-PGHS Antibodies

Two anti-PGHS antibodies (antibodies 8223 and
MF243) were used. Affinity-purified polyclonal an-
tibody 8223 was raised in rabbits against ovine
PGHS-1 and was shown to be selective for PGHS-1
in various species (34,35). Antibody MF243 was
provided by Drs. Jilly F. Evans and Stacia Kargman
(Merck Frosst Centre for Therapeutic Research,
Pointe-Claire-Dorval, Québec). MF243 was raised
in rabbits against ovine placental PGHS-2, and its
selectivity for PGHS-2 has previously been charac-
terized (22).

Immunohistochemistry

Immunohistochemical staining was performed
with the use of the Vectastain ABC kit (Vector
Laboratories, Inc., Burlingame, CA), as previously
described (36). Briefly, formalin-fixed tissues were
paraffin embedded, and 3-μm-thick sections were
prepared and deparaffinized through graded alcohol
series. Endogenous peroxidase was quenched by in-
cubation overnight at 4 °C. Control sections were
incubated in 10% normal horse serum (n
4
5
0% of positive cells, 1
0% of positive cells, 2
10%–30% of positive cells, 3
31%–60% of positive cells, and 4
greater than 60% of positive cells. Also, the
intensity of PGHS-2 immunoreactivity was graded
as − = no staining, + = weak staining, ++ = moderate staining, and +++ = strong staining.

Solubilized Cell Extracts and
Immunoblot Analysis

Solubilized cell extracts were prepared as previ-
ously described (35). Briefly, tissues were homog-
enized on ice in TED buffer (50 mM Tris [pH 8.0],
10 mM ethylenediaminetetraacetic acid [EDTA], and
1 mM diethyldithiocarbamic acid [DEDTC]) contain-
ing 2 mM octyl glycoside and centrifuged at
30 000g for 1 hour at 4 °C. The crude pellets (mem-
branes, nuclei, and mitochondria) were sonicated (8
seconds per cycle; three cycles) in TED sonication
buffer (20 mM Tris [pH 8.0], 50 mM EDTA, and 0.1
M DEDTC) containing 32 mM octyl glycoside.
The sonicates were centrifuged at 16 000g for 15
minutes at 4 °C. The supernatant (solubi-
lized cell extract) was stored at −70 °C until electro-
phoretic analyses were performed. The protein con-
centrations were determined by the method of
Bradford (37) (Bio-Rad Protein Assay). Proteins
were resolved by one-dimensional sodium dodecyl
sulfate–polyacrylamide gel electrophoresis (SDS–
PAGE) and electrophoretically transferred to nitro-
membranes (21). The intensity of PGHS-2 expres-
sion between normal pros-
states and prostatic adenocarcinomas. All P values
reported are two-sided. Statistical analyses were
performed with the use of the JMP Software (SAS In-
stitute, Inc., Cary, NC).

RESULTS

Characteristics of dogs with prostatic
adenocarcinomas. The age of the dogs
with prostatic adenocarcinoma ranged
from 5.5 to 15 years old, with a mean of
9.6 years. Of the 24 case animals,
13 (54%) were castrated, five (21%)
were intact, and the neuter status of six
animals was unavailable. No breed predi-
cision was observed (Table 1). At the
time of diagnosis, a high percentage of
dogs (14 [58%] of 24) had metastases to
various organs, most frequently to the ab-
dominal serosa, lungs, and lymph nodes
(Table 1).

PGHS-1 expression in normal ca-
nine prostates. To determine whether
PGHS-1 and/or PGHS-2 were expressed
under physiologic conditions, we per-
formed immunohistochemical staining on
normal canine prostates (n = 4). Results
showed that PGHS-1 was present in fibro-
blastic cells of the conjunctive stroma and
in endothelial cells of some blood vessels
(Fig. 1, A and B) in all four normal pros-
states. However, no PGHS staining was
observed in prostatic epithelial cells (Fig.
1, C), and no PGHS-2 expression was
detected in normal canine prostates (Fig.
1, D).

Induction of PGHS-2 in canine pro-
static adenocarcinomas. A different
staining pattern was observed in prostatic
adenocarcinomas. In contrast to normal
prostates where no PGHS-2 was detected,
18 (75%) of the 24 adenocarcinomas
studied expressed PGHS-2 (P = .01;
Table 1). PGHS-2 was observed in 12 of
13 castrated dogs and in four of five intact
dogs. PGHS-2 expression was localized
to epithelial tumor cells (Fig. 2, A–D).
The intensity of the reaction varied
among tumors (Table 1), ranging from a
diffuse pale cytoplasmic positive staining
to a very strong reactivity filling the cell.
In some cells, the PGHS-2 staining
formed a discrete perinuclear halo (Fig. 2,
C and D). As observed in normal pros-
states, PGHS-1 was detected in the major-
ity of adenocarcinomas (22 of 24 case
animals) in stromal fibroblasts and/or vas-
cular endothelial cells. Also, a faint
PGHS-1 signal was observed in epithelial
cells in some tumors (Fig. 2, E). No stain-
ing was detected in control sections with
the use of normal rabbit serum (Fig. 2, F)
or PBS (data not shown).

Immunoblotting of PGHS isoen-
zymes in canine prostate tissues. To
document the specificity of anti-PGHS
antibodies on canine tissues and charac-
terize each PGHS isoenzyme in the dog,
we prepared solubilized cell extracts from
normal prostates, prostatic adenocarcino-
mas, and platelets, and we analyzed pro-
teins by western blotting. When a selec-
tive anti-ovine PGHS-1 antibody was
used, a 69 000-molecular-weight (M
) band was detected in normal prostates
and in prostatic adenocarcinomas (Fig. 3, A).
A band of identical molecular weight was
detected in canine platelets (Fig. 3, A) and
thus corresponded to canine PGHS-1. In
contrast, when a selective anti-ovine
PGHS-2 antibody was used, no signal was
detected in normal prostates, but PGHS
immunoreactivity was observed in pros-
tatic adenocarcinomas (Fig. 3, B). Canine PGHS-2 appeared as a 72 000- to 74 000-
Mr doublet and a small 62 000-Mr band (Fig. 3, B) believed to correspond to a proteolytic fragment, as previously observed in other species (16,34,35). The absence of detectable PGHS-2 in canine platelets is in keeping with reports in other species (18). The precise nature of smaller and weaker immunoreactive bands detected in Fig. 1, A and B, is unknown, but it is thought to represent fragments of PGHS proteins.

**DISCUSSION**

To our knowledge, this study demonstrates for the first time the induction of PGHS-2 in a high percentage of cancerous prostatic tumors. Whereas no PGHS-2 was detected in normal prostates, 75% of prostatic adenocarcinomas contained epithelial tumor cells expressing PGHS-2. PGHS is the key rate-limiting enzyme in the biosynthetic pathway of prostaglandins from arachidonic acid, and increasing evidence (38–42) supports a role for prostaglandins in prostate carcinogenesis. The administration of indomethacin, a potent PGHS inhibitor, to rats bearing subcutaneous implants of an androgen-insensitive prostate adenocarcinoma was shown to reduce tumor size, metastatic rate, and mortality (38). Inhibitors of eicosanoid biosynthesis have also

**Table 1. Characteristics of specimens from dogs with prostatic adenocarcinomas**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y</th>
<th>Breed</th>
<th>Neuter status</th>
<th>Presence of metastasis</th>
<th>PGHS-2 staining</th>
<th>Grade†</th>
<th>Intensity‡</th>
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<td>1</td>
<td>15</td>
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<td>Yes</td>
<td>N/A</td>
<td>4</td>
<td>+++</td>
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<td>2</td>
<td>7</td>
<td>Husky</td>
<td>Yes</td>
<td>Lung</td>
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<tr>
<td>3</td>
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<td>N/A</td>
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<td>++</td>
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<td>4</td>
<td>11</td>
<td>Miniature Schnauzer</td>
<td>No</td>
<td>Lymph nodes, heart, lung, kidney, and skin</td>
<td>4</td>
<td>+++</td>
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<tr>
<td>5</td>
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<td>Skin</td>
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<td>6</td>
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<tr>
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<td>10</td>
<td>Mixed breed</td>
<td>Yes</td>
<td>Lung, bone, and lymph node</td>
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<td>+++</td>
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<tr>
<td>8</td>
<td>7.5</td>
<td>Shetland Sheepdog</td>
<td>Yes</td>
<td>No</td>
<td>3</td>
<td>+++</td>
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<tr>
<td>9</td>
<td>14</td>
<td>Dax Red</td>
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<td>N/A</td>
<td>3</td>
<td>+++</td>
<td></td>
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<tr>
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<td>12</td>
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<td>N/A</td>
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<td>++</td>
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<tr>
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<td>7</td>
<td>Bulldog</td>
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<td>Abdominal serosa</td>
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<tr>
<td>12</td>
<td>8</td>
<td>Beagle</td>
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<td>+++</td>
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<tr>
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<td>12</td>
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<td>15</td>
<td>10.6</td>
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<td>–</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>8</td>
<td>Mixed breed</td>
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<td>Abdominal serosa</td>
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<td>+++</td>
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<td>N/A</td>
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<td>++</td>
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<tr>
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<td>7</td>
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<td></td>
</tr>
</tbody>
</table>

* N/A = information not available; PGHS-2 = prostaglandin G/H synthase-2.
† 0 = 0%, 1 = <10%, 2 = 10%–30%, 3 = 31%–60%, and 4 = >60% of positive cells.
‡ − = no staining, + = weak staining, ++ = moderate staining, and +++ = strong staining.

**Fig. 1.** Expression of prostaglandin G/H synthase-1 (PGHS-1) by normal canine prostates. Immunohistochemistry was performed on formalin-fixed sections of normal canine prostates, as described in the “Materials and Methods” section. Immunostaining with antibody 8223 (selective for PGHS-1) demonstrated the presence of PGHS-1 in the stroma and in the endothelium of blood vessels (A and B) but not in epithelial cells (C). Immunostaining with antibody MF243 (selective for PGHS-2) showed no reactivity in the stroma or in epithelial cells (D) (original magnifications ×200 [A] and ×400 [B–D]).
been reported to inhibit cellular proliferation of some human prostate cancer cell lines (39,40). It has been shown that malignant prostatic tissues have lower concentrations of arachidonic acid and produce more prostaglandin E2 \textit{in vitro} when compared with benign prostatic tissues (41). Faas et al. (42) showed that phospholipase A2 activity and fatty acyl-CoA lysophosphatidylcholine acyltransferase activity are increased in prostate cancer and proposed that increased prostaglandin synthesis may be important for the growth of malignant prostatic tissues.

Recent studies indicate that PGHS-2, the inducible form of the enzyme, is implicated in the production of prostaglandins by cancerous cells from a variety of tissues. Increased expression of PGHS-2 was first demonstrated in human colorectal cancers but has now been reported in tumor cells from pulmonary, gastric, skin, esophageal, and breast carcinomas (22–26,43). Increased expression of PGHS-2...
messenger RNA has been shown in two human prostate cancer cell lines (29), but the expression of PGHS-2 by prostate cancer cells in vivo has not been documented. The potential role played by PGHS in cancer is underscored by the finding that the long-term use of aspirin and other NSAIDs appears to significantly decrease the relative risk for certain types of cancer, notably colorectal cancer (8–10,44). Aspirin is known to acetylate and irreversibly inactivate PGHS enzymes (45). Epidemiologic studies (46,47) investigating aspirin use in relation to various cancers have reported weak inverse associations for prostate cancer risk. A recent population-based, case–control study (31) aimed at specifically investigating a possible association between prostate cancer risk and NSAIDs found an inverse association between the risk of advanced prostate cancers and the regular use of aspirin and other NSAIDs.

The mechanisms by which increased synthesis of PGHS contributes to tumor development are slowly beginning to unravel. Studies in vitro have shown that intestinal epithelial cells overexpressing PGHS-2 exhibit increased adhesion to extracellular matrix and are resistant to induced apoptosis, two phenotypic changes that could enhance their tumorigenic potential (48). It is interesting that Liu et al. (30) recently reported that a selective PGHS-2 inhibitor, NS398, induced apoptosis and caused a decreased synthesis of bcl-2 (an antiapoptotic oncoprotein) in a human prostate cancer cell line. Expression of PGHS-2 could also be associated with increased metastatic potential, as suggested by the increased invasiveness of a human colon cancer cell line transfected with a PGHS-2 expression vector (49). The same group of authors (50) also recently presented evidence that colon cancer cells overexpressing PGHS-2 produce high levels of angiogenic factors that could contribute to tumor angiogenesis, a step essential to tumor growth. They (50) suggested that PGHS-2 modulates production of angiogenic factors by cancer cells, while PGHS-1 in endothelial cells plays a role in endothelial tube formation. Furthermore, prostaglandins are known to contribute to cancer development by acting at different levels of malignant transformation, including stimulation of cell growth, involvement in tumor promotion, and suppression of the immune response (8,51).

Although prostate cancer represents the most common male cancer in the United States, the factors responsible for its high prevalence are poorly understood. In men, prostate cancer is influenced by age, race, and certain environmental, dietary, and familial factors (52). However, very little is known about the molecular mechanisms leading to prostate cancer. For reasons not yet understood, the dog is the only nonhuman species that frequently develops spontaneous prostate cancer with advancing age (2). Of interest, many aspects of canine prostate cancer are similar to the human disease (3,4). For example, prostate cancer is strongly influenced by age in both species. A study (53) has shown that the physiologic age at prostate cancer diagnosis, expressed in human years, was similar between the two species (67 and 70 years for dogs and men, respectively). Also, certain premalignant and malignant changes at the histologic level are similar in both species, including the presence of high-grade prostatic intraepithelial neoplasia in canine prostate (5,6). This premalignant change has been reported in the prostate of normal dogs and in dogs with spontaneous prostate carcinoma (5,6). In normal dogs, the prevalence of high-grade prostatic intraepithelial neoplasia seems to be influenced by age and testicular androgens (5). Moreover, prostate cancer in dogs displays a high incidence of osseous metastases, as observed in men (3). These similarities were underscored in a recent international workshop on animal models of prostate cancer that proposed the dog model is a reproducible model of prostate cancer (5). The induction of PGHS-2 in a majority of canine prostatic adenocarcinomas provides a novel element in our understanding of prostate cancer in dogs. Further study of PGHS-2 may provide insight into human prostate carcinogenesis and progression.

REFERENCES


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