adenylyl cyclase (*20*, *25*), the ability to activate phospholipase C (*25*). In sG_{i2} this whole region is substituted by a different 35–amino acid segment. This segment confers on sG_{i2} a subcellular localization different from that of G_{i2}. This mechanism closely resembles that for localization of members of the Rab family (*27*), small GTP-binding proteins also implicated in intracellular transport. The exchange of the COOH-terminal 35 amino acids between Rab5 and Rab7, two proteins localized in the early and late endosomes, respectively, retargets them to the subcellular compartment associated with the corresponding COOH-terminus (*27*). The COOH-terminus may recognize specific receptors in the appropriate compartment.

The presence of the alternative COOH-terminal domain in sG_{i2} may imply the existence of organelle-specific receptors involved in its recognition. The function of this protein might be synergistic with that of other GTP-binding proteins in the regulation of membrane transport mechanisms.

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15. For PCR analysis cDNA from mouse pituitary RNA was prepared (*20*) with 2 μg of total RNA. A portion of the reverse transcribed RNA was then used for PCR reactions. In each reaction 5′ and 3′ oligonucleotide primers (1 μg of each) were used. The 5′ oligonucleotide sequence GCCAACAAG-TACGACGAGGCA corresponds to position 879 to 899 of the G_{i2} coding sequence. The 3′ oligonucleotide corresponds to the last 18 nucleotides of the sG_{i2} coding region illustrated in Fig. 1C. To amplify mouse genomic DNA, we used 500 ng of intact DNA. The DNA was previously denatured at 94°C for 10 min. PCR was done under the same conditions used to amplify the cDNA described elsewhere (*21*). PCR products were separated on agarose gels, blotted, and hybridized with a ^{32}P-labeled oligonucleotide probe corresponding to the first 18 nucleotides of the sG_{i2} translated sequence in exon 9 (Fig. 1C).
16. The sG_{i2} cDNA fragment from the Bam HI site at position 634 to 20 base pairs (bp) 3′ from the TGA was inserted into the Hind II site of the pBluescript polylinker. The plasmid DNA was linearized at the Bgl II site, and a uniformly labeled antisense transcript was synthesized from the T3 RNA polymerase promoter, incorporating [α-^{32}P]uridine triphosphate. RNA probes were obtained with a Riboprobe kit (Promega). The ribonuclease protection assays were done as described (*28*).
17. The cDNAs corresponding to G_{i2} and sG_{i2} were subcloned in the Not I site of the expression vector p513 (*11*), linearized, and transcribed in vitro with T7 RNA polymerase. Purified RNA was then translated and labeled in vitro with a rabbit reticulocyte lysate system (Promega) including [^{35}S]methionine (Amersham). The products were analyzed on 10% polyacrylamide gel. Immunoprecipitations were done as in J. R. Barber and I. Verma, [*Mol. Cell. Biol.* **7**, 2201 (1987)].
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29. COS-7 cells were fixed in acetone:methanol and incubated overnight with the specific antibody at the appropriate dilution. No specific staining was obtained when sG_{i2} was preincubated with an excess amount of the peptide used to obtain the antibody. The antibody 293 was visualized with Texas red–labeled goat antibody to rabbit immunoglobulin G. The M3A5 mouse monoclonal antibody was revealed by fluorescein–labeled goat antibody to mouse immunoglobulin G. The secondary antibody used for sG_{i2} was also used with AS7. The Bodipy ceramide (Molecular Probes, Oregon) staining of living COS-7 cells was done as in (*23*).

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The Met Proto-Oncogene Mesenchymal to Epithelial Cell Conversion

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Coexpression of the human Met receptor and its ligand, hepatocyte growth factor/scatter factor (HGF/SF), in NIH 3T3 fibroblasts causes the cells to become tumorigenic in nude mice. The resultant tumors display lumen-like morphology, contain carcinoma-like focal areas with intercellular junctions resembling desmosomes, and coexpress epithelial (cytokeratin) and mesenchymal (vimentin) cytoskeletal markers. The tumor cells also display enhanced expression of desmosomal and tight-junction proteins. The apparent mesenchymal to epithelial conversion of the tumor cells mimics the conversion that occurs during embryonic kidney development, suggesting that Met-HGF/SF signaling plays a role in this process as well as in tumors that express both epithelial and mesenchymal markers.

The *met* proto-oncogene product (Met) is a member of the family of tyrosine kinase growth factor receptors (*1*, *2*), and its ligand is hepatocyte growth factor/scatter factor (HGF/SF) (*3*–*5*). HGF/SF mediates liver regeneration in vivo (*6*), induces differentiation of Madin-Darby canine kidney (MDCK) epithelial cells into branching tubules (*7*), and promotes epithelial cell motility and invasiveness in vitro (*5*, *8*). Two lines of evidence (*9*) suggest that Met is involved in the formation and maintenance of epithelial lumenal structures: (i) Met is expressed in epithelial cells bordering lumenal structures in a variety of tissues, including cells that border the mammary duct, and (ii) treatment of certain carcinoma cell lines with human HGF/SF (HGF/SF^{hu}) induces the formation of lumenal structures in vitro.

NIH 3T3 cells produce murine HGF/SF^{mu}

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endogenously and become highly tumorigenic through an autocrine mechanism when they are engineered to overexpress murine Met. Likewise, NIH 3T3 cells coexpressing Met^{hu} and HGF/SF^{hu} [HMH cells (*10*)] are highly tumorigenic (*11*, *12*). Explants of HMH tumors cultured on glass (*10*) formed lumenal structures (*13*) (Fig. 1, B and C) that were indistinguishable from lumens formed by HGF/SF^{hu}-treated epithelial carcinoma cells in vitro (*9*). This result was unexpected because lumen formation has not been observed with cells of mesenchymal origin. Lumenal structures were not observed with the parental NIH 3T3 cells or with MT cells, a control cell line overexpressing the Met^{hu} receptor (*10*) (Fig. 1A). The Met^{hu} product is not activated in MT cells (*11*); however, the treatment of MT cells with HGF/SF^{hu} ligand (10 ng/ml) induced lumen formation in vitro (*14*) at a much lower frequency than observed with the autocrine-stimulated HMH cells. The treatment of parental NIH 3T3 cells with HGF/SF^{hu} did not induce lumen formation (*14*). Epithelial-like morphology has been reported for NIH 3T3 cells transfected with met^{hu} and treated with HGF/SF^{hu} (*15*).

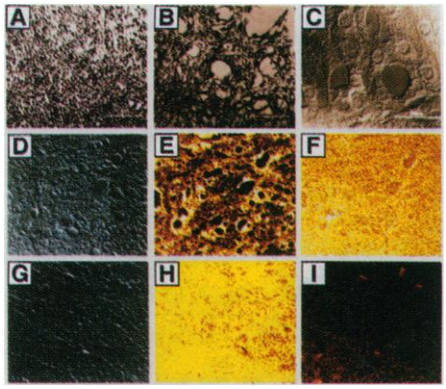

Fig. 1. Formation of lumen-like structures by HMH tumor cells in vitro and in vivo. (**A** to **C**) Cells were grown to ~90% confluence and fixed and stained with methylene blue before CLSM analyses. Nomarski view of: (A) NIH 3T3 cells and (B) HMH cells; (C) is a high magnification of (B). Scale bar, 250 μm. (**D** to **I**) Paraffin-embedded sections of HMH and MT tumors. Nomarski view of (D) HMH and (G) MT sections. (E) HMH and (H) MT sections stained with the C28 antibody to Met^{hu}; (F) HMH and (I) MT tumor sections stained with an antibody to HGF/SF. Note the intense Met^{hu} staining around the lumenal structures in (E). Magnification, ×85 in (D) to (F).

To determine whether HMH tumors form lumens in vivo, we examined the tumors by confocal laser-scanning microscopy (CLSM) (*16*). Lumenal structures were observed at high frequency in HMH, but not MT, tumors (*10*) (Fig. 1, D and G) or in tumors produced by the aberrant expression of *ras* and *src* (*14*). Both the HMH and MT tumor cells stained with an antibody to Met^{hu} (*2*, *16*) (Fig. 1, E and H), whereas the HMH, but not the MT, tumor cells stained with an antibody to HGF/SF (*17*) (Fig. 1, F and I). Toluidine blue–stained sections of the HMH tumors (*18*) contained areas with a trabecular pattern that was more characteristic of an epithelial adenocarcinoma (Fig. 2A) than of the fibrosarcomas that typically develop from oncogene-transformed NIH 3T3 cells. In each of 10 HMH tumors examined, we observed carcinoma-like focal areas that displayed typical epithelioid cell clusters. The autocrine-activated Met^{mu} tumors also displayed carcinoma-like areas, but at a lower frequency (*14*). Met^{mu} tumors develop more rapidly than the HMH tumors (*11*), and this difference may play a role in the conversion to the carcinoma morphology.

Examination of the HMH tumors by transmission electron microscopy (TEM) (*18*) revealed that the tumor cells are connected by junctional complexes resembling desmosomes (Fig. 2B). We determined that the cells forming desmosomes were derived from the HMH tumor, because they were positive for Met^{hu} expression (Fig. 2B). The presence of desmosomes provided further evidence that the HMH tumor cells had converted to a carcinoma morphology.

We then tested HMH and MT tumors for the expression of two different intermediate filament proteins—cytokeratin, an epithelial-specific protein that is anchored to desmosomes, and vimentin, a mesenchymal-specific protein that is normally expressed by NIH 3T3 fibroblasts. Cytokeratin was highly expressed in the HMH tumors but not in the MT control tumors (*10*), whereas vimentin was expressed in both HMH and MT tumors (Fig. 3A). The HMH tumor stained with the C28 antibody to Met^{hu} (Fig. 3A), confirming that this tumor arose from HMH cells. The frequent formation of lumenal structures in the HMH sections was revealed in the Nomarski view (Fig. 3A). Both Met staining and cytokeratin staining were intense in the cells bordering the lumen (*9*); in contrast, the vimentin staining did not localize to these structures (Fig. 3). In addition, the HMH tumors showed markedly enhanced expression of proteins involved in epithelial intercellular interactions, such as the desmosomal proteins, desmoplakin and desmoglobin (*19*); ZO-1, a tight junction protein (*20*); and E-cadherin, an actin cytoskeletal–associated protein (Fig. 3B). The expression of these proteins was much lower or absent in the MT tumor (Fig. 3B). Both HMH and MT tumors expressed high levels of Met^{hu} (Fig. 3). It has been proposed that the same molecular mechanisms that control epithelial cell dissociation ("scattering") also control lumen formation (*9*, *21*) and that both these processes may involve actin cytoskeletal and adhesion proteins that shape cell morphology and promote intercellular interactions (*21*). Our results support this view, in that the activation of Met by its ligand in mesenchymal cells was shown to induce lumen formation and the expression of E-cadherin, ZO-1, and desmosomal proteins.

The acquisition of epithelial properties by the fibroblast-derived HMH cells mimics the mesenchymal to epithelial conversion of cells during the organogenesis of the kidney, ovary, and testis. These differentiating cells express both vimentin and cytokeratin during embryonic development (*22*, *23*), and Met expression is high in both the embryonic and adult kidney (*14*, *24*). We therefore investigated whether Met^{mu} is coexpressed with vimentin and cytokeratin in the developing kidney. Serial sections of an 11.5-day mouse embryo were stained with an antibody to Met^{mu} (*9*,

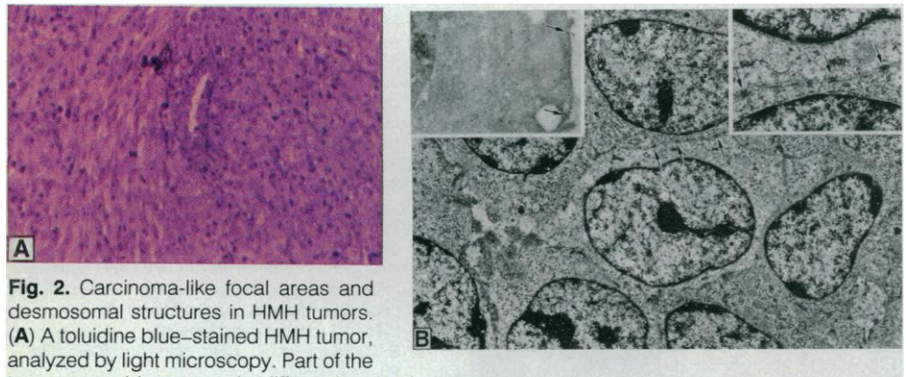

Fig. 2. Carcinoma-like focal areas and desmosomal structures in HMH tumors. (**A**) A toluidine blue–stained HMH tumor, analyzed by light microscopy. Part of the tumor resembles a poorly differentiated adenocarcinoma, containing polygonal, darkly stained cells, islands of glandular cells, and minimal connective tissues (right). Other parts of the tumor retain the spindle-shaped fibrosarcoma pattern typical of tumors derived from NIH 3T3 cells (left) (magnification, ×83). (**B**) The same tumor as in (A) analyzed by TEM (magnification, ×5200). Arrows indicate intercellular junctions resembling desmosomes (also visible in right inset at higher magnification, ×8500). Left inset is an analysis of the same tumor by immunogold electron microscopy with an antibody to Met^{hu}. Arrows indicate Met staining in the cells forming the desmosomes (magnification, ×5200).

24) and with antibodies to vimentin or cytokeratin before CLSM analysis (25) (Fig. 4). The developing kidney coexpressed vimentin, Met^{mu}, and cytokeratins (Fig. 4, A to C). In an adjacent region of the same embryo section, the vimentin-specific antibody stained only the mesenchymal portion of the gastrointestinal tissue (Fig. 4A, inset), whereas the cytokeratin-specific antibody stained only the epithelial cells and not the surrounding mesenchymal cells of the gastrointestinal tract (Fig. 4C, inset). These results suggest that Met and the HGF/SF signal transduction pathway are involved in the development of the embryonic kidney.

In adult tissues, intermediate filament proteins are expressed in a cell-type–specific manner. The coexpression of cytokeratins and vimentin is restricted to early development (26), except in wound healing (27) and in certain types of neoplasia (28). It has been postulated that in wound healing, the cells expressing both intermediate filament classes are dedifferentiated epithelial cells or are derived from mesenchymal cells that are converted into tubular epithelial cells (23). Our results support the latter hypothesis. We propose that the HGF/SF-mediated activation of Met in mesenchymal cells at the wound site may play a role in converting these cells to an epithelial phenotype.

Cells that coexpress cytokeratin and vimentin in certain carcinomas are thought to originate from epithelial cells that dedifferentiate and synthesize vimentin or from epithelial cells that differentiate from a primordial mesenchymal cell type (23). Giant-cell lung carcinomas (29), ductal and mucinous adenocarcinomas of the breast (30), and epithelial portions of kidney tumors also express vimentin (31). We propose that the inappropriate expression of Met in certain mesenchymal cells can lead to a carcinogenic transformation in which the tumor cells express both mesenchymal and epithelial markers (32). Carcinomas that coexpress cytokeratin and vimentin may originate by cell conversion, as observed in the carcinoma-like region of the HMH tumors. However, we cannot exclude the possibility that other growth factors and receptors are also required for this conversion.

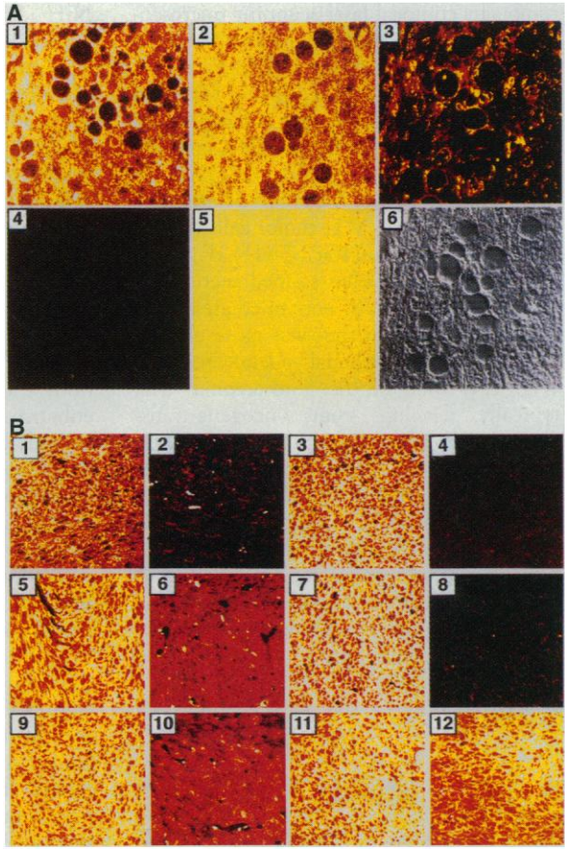

Fig. 3. Expression of cytokeratins by HMH tumor cells in vivo. (**A**) Paraffin-embedded sections of HMH tumors were examined by CLSM after staining with antibodies to cytokeratin (1) or vimentin (2). MT tumors were similarly stained with antibodies to cytokeratin (4) or vimentin (5). Also shown is a Nomarski view (6) and Met^{hu} antibody staining (3) of the HMH tumor (magnification, ×190). (**B**) Staining of HMH tumors with antibodies to epithelial cytoskeletal and adhesion proteins. Paraffin-embedded sections of HMH (1, 3, 5, 7, 9, 11) or MT (2, 4, 6, 8, 10, 12) tumors were examined by CLSM after staining with antibodies to desmosomal proteins (1 and 2), desmoplakin (3 and 4), desmoglobin (5 and 6), ZO-1 (7 and 8), E-cadherin (9 and 10), and Met^{hu} (11 and 12) (magnification, ×95).

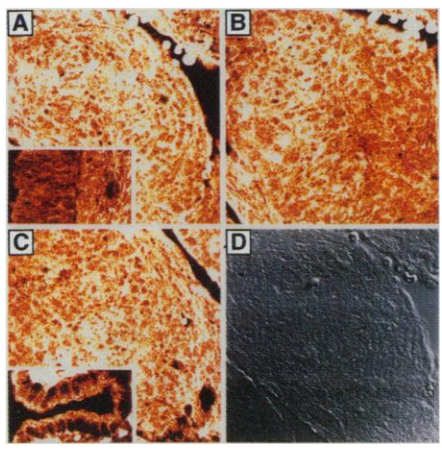

Fig. 4. Met expression during mesenchymal to epithelial cell conversion in the developing mouse kidney. Paraffin-embedded serial sections of 11.5-day embryonic mouse kidneys were examined by CLSM for the expression of (**A**) vimentin, (**B**) murine Met^{mu}, and (**C**) cytokeratin. The specificity of the vimentin and cytokeratin staining is shown in an adjacent region of the embryo that specifically expresses vimentin [submucosal connective tissue of the developing gastrointestinal tract (inset, A)] or cytokeratin [lumen of the gastrointestinal tract (inset, C)] (magnification, ×67). (**D**) Nomarski view of the embryonic kidney.

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10. All tumors were derived from NIH 3T3 cells transfected with complementary DNAs (cDNAs) driven by a long terminal repeat (LTR) promoter (*11*). Murine Met (Met^{mu}) tumors arose from cells transfected with a *met*^{mu} cDNA. HMH tumors arose from cells cotransfected with *met*^{hu} and *HGF/SF*^{hu} cDNAs. MT tumors arose from cells transfected with *met*^{hu} cDNA. The latter cells are normally not tumorigenic, but did produce tumors in one experiment (*11*). These rare tumors were most likely due to some form of oncogene activation rather than autocrine-mediated tumorigenesis, and we have therefore used the MT cells and tumors as controls in our experiments. HMH and MT tumors were generated in nude mice by the injection of ~10^6 tumor explant cells. Animals were killed when palpable tumors had formed (~14 days).
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13. In vitro lumen formation assays were performed as in (*9*). NIH 3T3 and MT (*10*) cells were plated directly or treated during plating with HGF/SF^{hu} (10 ng/ml) prepared as in (*12*); HMH cells were plated directly. The cells were visualized and photographed with a Zeiss LSM-310.
14. I. Tsarfaty, unpublished results.
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16. Fixed cells or paraffin-embedded tissue sections were stained with hematoxylin and eosin (H&E) and examined by light microscopy or immunostained as in (*9*). We used primary antibodies to Met^{hu} [C28, a rabbit antibody that does not cross-react with Met^{mu} (*9*); 1:100 dilution in phosphate-buffered saline (PBS)]; pan-cytokeratin (1:20 dilution, Amersham); vimentin (1:20 dilution, Amersham); HGF/SF [1:1 dilution (*17*)]; E-cadherin

(Zymed); plakoglobin (Pierce); desmosomal proteins (Sigma); desmoplakin (ICN, Cleveland, OH); and ZO-1 (Zymed). Incubations with secondary antibodies [donkey antibodies to rabbit or to mouse immunoglobulin coupled to fluorescein isothiocyanate] and visualization of stained cells were as in (*9*). Photomicrographs were prepared with a Codonics (Middleburg Heights, OH) NP600 printer.
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18. Tumor tissue was surgically excised, fixed in formaldehyde (formalin), embedded in paraffin, sectioned, and stained with antibodies (*16*) or with 1% toluidine blue. For TEM, solid tumor areas were identified and cut from the paraffin block, deparaffinized, cut into 0.5-mm^3 cubes, fixed in 2.5% glutaraldehyde for 2 hours at 4°C, washed four times with PBS for 30 min each, and post-fixed with 1% osmium tetroxide for 1 hour at 4°C. After washing with PBS, the samples were dehydrated in an acetone series and embedded in Epon 812 (Polyscience, Warrington, PA). Sections were cut with an LKB NOVA (Uppsala, Sweden) ultramicrotome. Semi-thin sections were cut with a glass knife and stained with 1% toluidine blue in 1% borax. Thin sections were cut with a diamond knife. Post-embedding immunoelectron microscopy was performed as in (*9*).
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25. Serial sections of 11.5-day mouse embryos were processed as in (*16*) but were stained with antibodies to Met^{mu} (SP260) (*9, 24*), cytokeratin (1:20 dilution), or vimentin (1:20 dilution). Immunofluorescence was analyzed by CLSM (*16*).
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