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Apolipoprotein J expression at fluid–tissue interfaces: Potential role in barrier cytoprotection

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ABSTRACT **Apolipoprotein J (apoJ) is a sulfated secreted glycoprotein that exhibits ubiquitous expression, evolutionary conservation, and diverse tissue inducibility. It has been proposed to have roles in programmed cell death, sperm maturation, complement regulation, and lipid transport. To identify cell types that synthesize apoJ and to aid evaluation of its function, we screened mouse and human tissues by *in situ* hybridization. ApoJ was expressed at high levels in an array of specialized cell types of adult and fetal mouse tissues and in similar cell types of human tissues. Most of these cell types are highly secretory and form the cellular interfaces of many fluid compartments. This group includes epithelial boundary cells of the esophagus, biliary ducts, gallbladder, urinary bladder, ureter, kidney distal convoluted tubules, gastric glands, Brunner's glands, choroid plexus, ependyma, ocular ciliary body, endometrium, cervix, vagina, testis, epididymus, and visceral yolk sac. Several nonepithelial secretory cell types that express high levels of apoJ also line fluid compartments, such as synovial lining cells and ovarian granulosa cells. In the context of its known biochemical properties, this expression pattern suggests that localized synthesis of apoJ serves to protect a variety of secretory, mucosal, and other barrier cells from surface-active components of the extracellular environment.**

Apolipoprotein J (apoJ[¶]) is an intriguing, ubiquitous, and highly conserved protein thought to be involved in a variety of biological processes, including lipid transport, sperm maturation, regulation of the complement cascade, programmed cell death, and membrane recycling (for review, see ref. 1). Its expression is induced in several pathological conditions, including neurodegenerative processes (2, 3) and testosterone withdrawn prostatic involution. Mature apoJ is a heterodimer composed of disulfide-linked subunits (Jα, $\approx$35 kDa; Jβ, $\approx$37 kDa) derived by proteolysis of a 70-kDa precursor subjected to post-translational processing and intracellular trafficking in a number of different cell types (4–10). ApoJ is present in numerous physiological fluids, such as urine, breast milk, cerebrospinal fluid (4, 11), semen, and human plasma (4, 12, 13). In plasma apoJ is present in high-density lipoproteins associated with lipid and apoA1 (12, 14, 15).

Speculations about apoJ function have been based on its interactions and biochemical properties and only limited information about its tissue expression pattern. The mRNA is present in nearly all mammalian tissues, albeit at different levels. Evaluation of the cellular sites of its synthesis has been limited to only a few organ systems—chiefly, the testes and kidney (16–21). To gain insight into potential physiological role(s) of apoJ, we used *in situ* hybridization to localize its sites of synthesis. The results indicate a striking expression of apoJ in highly restricted epithelial and other secretory cell types in diverse tissues. This expression pattern suggests that apoJ has a basic physiologic function common to diverse cell types that cannot be explained by some of the specialized functions proposed for apoJ in any single organ. Because of its unique biochemical properties, apoJ is likely to be particularly important to certain mucosal epithelial and other barrier cells exposed to potentially damaging agents present in complex aqueous environments. We propose that the primary function of apoJ is to stabilize cell membranes at diverse fluid–tissue interfaces.

MATERIALS AND METHODS

For *in situ* hybridization, mouse and human apoJ sense and antisense RNA probes were synthesized with ^{35}S-labeled rUTP from plasmids that contained the 1.4-kb mouse apoJ cDNA insert from clone 5-1 (S.D.L. and J.A.K.H., unpublished results) or the 741-bp fragment from the 3′ of the human apoJ cDNA from clone λ1-3 (8). CD-1 mice and human tissues were perfused and fixed overnight in 4% (wt/vol) paraformaldehyde in phosphate-buffered saline, cryoprotected, and embedded. Sections (6–8 μm) were air-dried on silane-coated slides, postfixed, prehybridized, hybridized, ribonuclease digested, and washed as described (22), using 0.1× standard saline citrate at 50°C (final stringency). Slides were exposed for 7–10 days.

RESULTS

Gastrointestinal Tract. Moderate and intense expression of apoJ mRNA was detected in many epithelial cell types of the mouse digestive system, but only in derivatives of the proximal gastrointestinal tract. Tongue mucosa was negative, but substantial apoJ mRNA was evident in mature epithelial cells of the esophageal and forestomach squamous mucosa (Fig. 1 *A* and *B*). Compared to more proximal forestomach squamous epithelium, glandular stomach mucosa exhibited much higher apoJ mRNA, specifically in glandular epithelial cells and mucin-secreting cells (Fig. 1*B*). Within single gastric glands, high expression occurred in chief cells (Fig. 1*C*), but not parietal cells. In the proximal stomach, mucin-secreting cells of the surface mucosa were strongly positive (Fig. 1*B*). However, in the more distal stomach, mucous cells at the surface were negative, but the mucous cells at the base of the glands were strongly positive. Brunner's glands, which occur only in the proximal duodenum and have been proposed to serve local and distal protective functions, exhibited intense apoJ signal (Fig. 1*D*). In contrast, no apoJ mRNA was

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Abbreviation: apo, apolipoprotein.

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¶ApoJ is synonymous with CLI (complement lysis inhibitor), clusterin, gp80, NA1/NA2, clone pADHC-9, SGP-2, SP-40, 40, and TRPM-2.

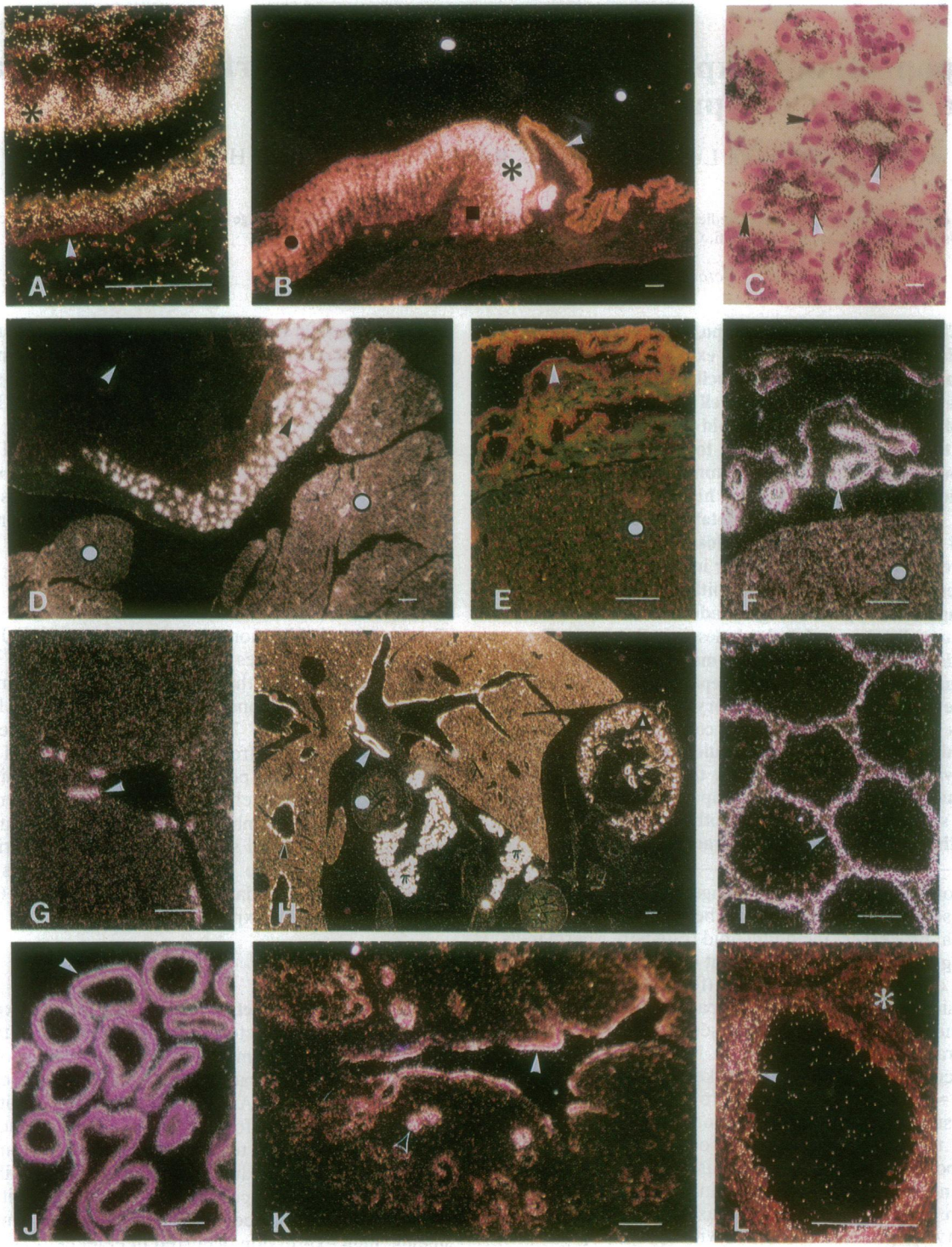
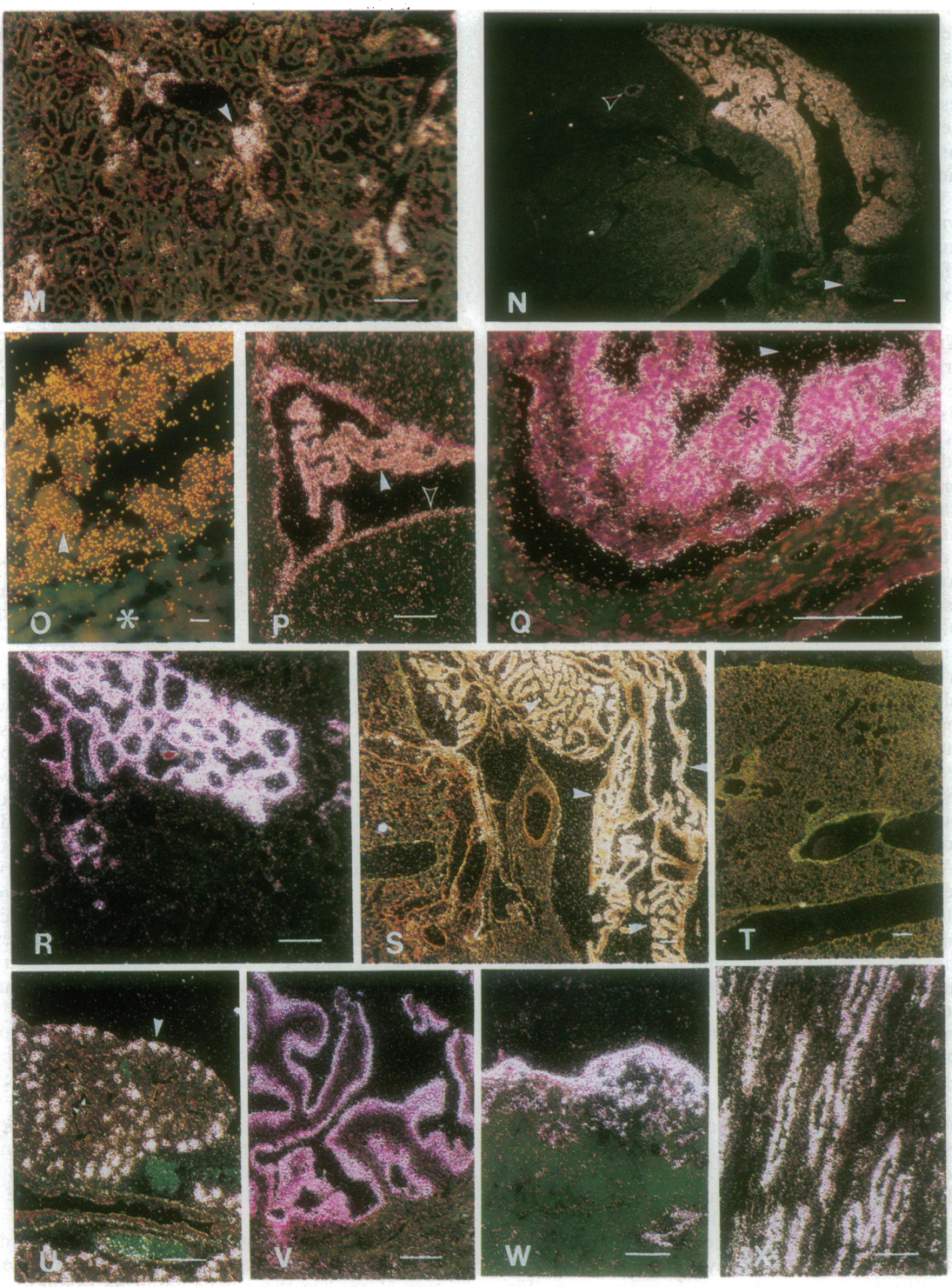


FIG. 1. Localization of apoJ expression by *in situ* hybridization. All tissues are from adult mouse except as indicated. (*A*) The esophagus shows signal (bright grains, *) that localizes to the superficial squamous epithelium. No signal is present in the germinal epithelial cells of the basal layer (arrowhead). (*B*) Low magnification of stomach, with squamous epithelial-lined forestomach on the right and glandular mucosa on the left. The forestomach shows moderate signal (arrowhead) in the superficial epithelium, similar to the esophagus. The more proximal glandular mucosa shows intense signal in the upper half (*), which includes the neck of the gastric glands and the mucin-containing surface cells. There is weaker signal in the lower half of the mucosal layer (square) where the gastric glands are located. In the more distal glandular mucosa to the left, the overall signal is less intense and restricted to the midportion of the mucosal layer (circle), which contains mostly mucin cells. (*C*) High magnification of stomach gastric glands from the proximal glandular mucosa. There are no grains over the acid-producing parietal cells (arrows), but the smaller chief cells show high-level apoJ expression (arrowheads). (*D*) In the duodenum there is strong signal only in the Brunner's glands (black arrowhead), with no signal in the overlying mucosal epithelium (white arrowhead). The acinar cells of the pancreas (circle) also show apoJ expression. (*E*) Sense-strand control is entirely negative in the gallbladder (arrowhead) and the liver (circle). (*F*) The gallbladder epithelium is strongly positive with antisense probe for apoJ (arrowhead), and there is diffuse signal in the liver (circle) shown in the lower half of the photomicrograph. (*G*) Higher magnification of liver, showing diffuse signal in hepatocytes and intense signal in the bile ducts (arrowhead) in the portal regions. (*H*) In a 17-day mouse embryo abdominal viscera, intense signal occurs in intra- (black arrowhead) and extra- (white arrowhead) hepatic biliary ducts, pancreatic glandular tissue (π), virtually all metanephric kidney tubules (Δ); moderate signal occurs in hepatocytes (λ); and no signal occurs in the small bowel



(white circle). (*I*) In the testis, signal is restricted to the Sertoli cell layer (arrowhead). (*J*) There is intense signal in the head of the epididymus in the tubular epithelial cells (arrowhead). (*K* and *L*) In the female genital tract, signal is present in the surface epithelial cells (white arrowhead) and glandular epithelium of the endometrium (black arrowhead) (*K*) and in the granulosa cell layers (arrowhead) lining an active ovarian follicle, but not in the adjacent inactive follicles (*) (*L*). (*M*) In the renal cortex, signal is only present in the distal convoluted tubular epithelium (arrowhead). (*N*) In the heart, strong expression occurs uniformly throughout the right atrium (*). No signal is present in the ventricle (left half of photomicrograph), but there is moderate signal over smooth muscle cells of the pulmonary artery (white arrowhead) and an intramural coronary artery (black arrowhead). (*O*) In a higher magnification of heart, signal occurs over the atrial myocytes (arrowhead) but not the ventricular myocytes (*). (*P*) In the brain, the ependymal lining (black arrowhead) and the choroid plexus epithelium (white arrowhead) are strongly positive. (*Q*) In the eye, the epithelial cells of the ciliary process (*) that project into the posterior chamber (arrowhead) are strongly positive. (*R*) In the Harderian gland, the active glands show intense apoJ message, but no signal is present in adjacent inactive glands. (*S*) In the placenta, pronounced expression occurs throughout the yolk sac membrane epithelial cells (arrowhead). (*T* and *U*) No signal is detectable in adult lung (*T*), but in 17-day fetal lung, there is intense signal in the periphery of the lobules within epithelial cells of the budding bronchioles (arrowheads), but not in the epithelial cells of mature bronchi (small arrowheads) (*U*). (*V–X*) In human tissues, a high level of apoJ was detected in gallbladder mucosal epithelial cells (*V*), synovial lining cells from a hip joint (*W*), and collecting tubular cells of the renal medulla (*X*). All sections have been counterstained with hematoxylin/eosin. (*C*) Bright-field illumination. (*A*, *B*, *D–X*) Dark-field illumination. (Bars: *A*, *B*, *D–N*, *P–X*, 100 μm; *C* and *O*, 10 μm.)

detected in any of the other cell types of the duodenum, jejunum, ileum, appendix, or colon.

Other gastrointestinal organs also expressed a high level of apoJ mRNA. In the liver, modest apoJ mRNA was present in hepatocytes compared to high-level expression in bile duct epithelial cells (Fig. 1 *F* and *G*). Pancreatic acinar cells were strongly positive, as were the pancreatic duct epithelial cells, extrahepatic biliary ducts, and gallbladder epithelium (Fig. 1 *D* and *F*). No apoJ mRNA was present in the pancreatic islets. Salivary glands such as the submaxillary gland did not express apoJ message except for occasional ductal epithelial cells. In a fetal mouse of 17-day gestation, a similar distribution of apoJ mRNA was seen in the gastrointestinal system (Fig. 1*H*).

Genital Tract. In the male genital tract, apoJ mRNA was highly restricted to several sites that have been described (19). In the testis (Fig. 1*I*), apoJ mRNA was limited to the Sertoli cells lining the seminiferous tubules. In the caput epididymus (Fig. 1*J*), intense apoJ signal was uniformly present in the epithelial cells lining all of the tubules. Less-intense signal occurred in the epithelial cells lining the ducts of the caudal epididymus (data not shown). No apoJ mRNA was evident in the vas deferens. In the prostate, only weak signal was evident in rare small prostatic ducts where they opened into the prostatic urethra. There was also no apoJ mRNA present in the seminal vesicle or Cowper's gland (data not shown).

In the female reproductive tract, strong apoJ signal was localized in the uterine endometrial surface epithelium and in endometrial glands (Fig. 1*K*) and similarly in epithelial cells in the fallopian tubes, endocervical, cervical, and vaginal mucosa (data not shown). Granulosa cells lining larger mature follicles also expressed apoJ message (Fig. 1*L*).

Urinary System. Abundant apoJ mRNA was evident in the cortex of the kidney, restricted to the epithelial cells lining the distal convoluted tubules (Fig. 1*M*). There was no detectable apoJ mRNA in the glomeruli, proximal, or medullary tubular epithelial cells. The transitional epithelium lining the calyces, pelvis, ureters, and bladder expressed moderate levels of apoJ message. The immature kidney differed from the adult kidney in that apoJ mRNA was present in virtually all of the primitive metanephric tubules and in the primitive epithelium lining the renal pelvis (Fig. 1*H*).

Other Organs and Tissues. In the heart, apoJ was strongly and uniformly expressed in myocytes of both the right (Fig. 1 *N* and *O*) and left atrium. No signal was detected in the ventricular myocardium. Weak apoJ signal was present in the smooth muscle cells in the wall of some large and medium-size arteries. In the brain, apoJ message was present in the epithelial cells of the choroid plexus, ependymal cells lining the ventricles (Fig. 1*P*), and the central canal of the spinal cord (data not shown). Also in the brain, a significant subpopulation of neurons and glial cells exhibited moderate expression (data not shown). In the eye, epithelial cells lining the ciliary body expressed a high level of apoJ message (Fig. 1*Q*). In adrenal cortical cells, moderate apoJ signal occurred in the glomerulosa layer and a weaker signal occurred in the fasiculata and reticularis layers (data not shown). ApoJ message was not detected in thyroid follicular cells or in the anterior pituitary (data not shown).

In the Harderian gland (Fig. 1*R*), a secretory gland in the posterior aspect of the orbit, strong signal was present. Glands that expressed apoJ message were lined by low cuboidal cells, had dilated lumens, and frequently contained pigmented secretions. These morphologic features are characteristic of actively secreting glands (23). Glands that did not express apoJ appeared to be inactive on the basis of their tall columnar lining, their small lumens, and the absence of secretions.

In the mature placenta (Fig. 1*S*), apoJ signal was present only in epithelial cells lining the visceral yolk sac membrane where it was very intense. ApoJ message was absent in mature lungs (Fig. 1*T*). The developing lung, however, showed strong apoJ expression in the epithelial cells lining the distal portions of the budding bronchioles and alveolar ducts (Fig. 1*U*). This expression disappeared in the lung 1–2 days prior to birth. The respiratory epithelium lining the trachea and larynx were also negative, but the submucosal glands in these organs expressed a high level of apoJ message (data not shown).

Human Tissues. In the limited number of human tissues studied, apoJ was expressed by many of the same cell types that exhibited expression in mice. Gallbladder showed intense signal, tightly restricted to the mucosal epithelial cells (Fig. 1*V*). In the liver, strong signal occurred in hepatocytes; intrahepatic bile ducts showed weaker signal compared to that seen in the mouse (data not shown). In synovial cells lining the hip joint, very strong apoJ signal was detected (Fig. 1*W*). The kidney showed strong signal in distal tubular epithelial cells in both the cortex and medulla (Fig. 1*X*).

DISCUSSION

ApoJ-expressing cells constitute a class of cell types defined by several striking features. Cells expressing high levels of apoJ occur over a wide anatomic range, but they are predominantly epithelial and tend to line compartments containing biologically active fluids such as gastric secretions, pancreatic juice, urine, bile, and Harderian gland secretion. Combining these observations with apoJ's known biochemical properties (for review, see ref. 24) suggests that apoJ regulates stability of the membrane boundary between fluid and tissue compartments. Mechanisms by which biliary epithelial cells (25) or cells of the Harderian gland (23, 26, 27), noted for their capacity to secrete bioactive and bactericidal lipids, can maintain their integrity are generally unknown. At these boundary interfaces, apoJ could contribute to the ability of cells to secrete or resist surface-active molecules.

The fact that similar cell types secreting similar products differ dramatically in apoJ expression suggests that the primary synthetic products of cells do not control or require apoJ expression. Surface mucous cells, for example, secrete carbohydrate-rich glycoproteins. Those in the stomach express apoJ, but distal bowel goblet cells do not. Similarly, mucinous epithelial cells of tracheobronchial submucosal glands express a high level of apoJ mRNA, but related mucous cells of tracheal surface epithelium do not. Heterogeneity in apoJ expression combined with other evidence (28) of phenotypic heterogeneity among tracheobronchial epithelial cells in distinct anatomic locations argues that components of the extracellular milieu determine the requirement for apoJ.

Several sites of high-level apoJ expression do not, however, appear to be exposed to harsh environments. Expression of apoJ in these cells could be required because of a specific product or class of products as yet unrecognized. If this were the case, the product is likely to be hydrophobic, as suggested by apoJ's strong propensity to aggregate (24) and the requirement for detergent to disrupt its interaction with apoAI and lipid (15) or chromaffin granule components (29). The high-level expression of apoJ in numerous sites exposed to bioactive and hydrophobic compounds predicts that high-expression sites not known to produce hydrophobic compounds, such as atrial myocytes that secrete atrial natriuretic factor and proenkephalin A via vesicles (30–32), are in fact exposed to membrane-active molecules. Alternatively, these cells may require apoJ to protect against cellular processes that destabilize focal membrane domains, e.g., membrane fusion.

A notable property of apoJ is its massive induction during programmed cell death in castration-mediated prostatic involution (33–36), in several models of kidney injury (36), and in neurodegenerative conditions of the brain (2, 3, 37, 38). Since our results document a constitutive pattern of apoJ expression in diverse cells unrelated to sites of cellular involution, it is unlikely that apoJ mediates programmed cell death. Skin, intestinal epithelium, and placental decidual cells contain large numbers of cells undergoing programmed cell death, but none of these tissues expresses apoJ mRNA at detectable levels. Other investigators have shown (39) a lack of correlation between apoJ and neuronal cell death. Thus, an attractive hypothesis is that apoJ induction is a reactive response to environmental changes rather than causative factor in cell death. In this manner, apoJ could be thought of as an extracellular version of a heat shock protein.

ApoJ has the biochemical potential to modify a number of biochemical processes at fluid–tissue interfaces. ApoJ inhibits complement-mediated lysis (4, 40, 41) and interacts with immunoglobulin (42). A variety of mucosal epithelial cells synthesize complement components (43–47), but the role of locally synthesized complement and complement inhibitors (48) is unclear. If the localized expression of these components determines important physiological and pathophysiological processes, then aberrant expression of apoJ could be deleterious. For example, human synovium, demonstrated here to be a site of high expression, also synthesizes a number of complement components in patients with degenerative joint diseases (49). Therefore, underexpression of apoJ could contribute to some types of joint disease. In the female reproductive tract where high levels of apoJ mRNA are expressed, complement produced by mucosal epithelial cells has been shown to mediate antibody-dependent sperm lysis (4, 6, 50). In this case, a failure to express apoJ could reduce fertility. Extension of our hypothesis of apoJ's protective role prompts consideration of whether increased expression of apoJ could be of benefit. For example, increased presence of the protein could act as an antiinflammatory agent in disease sites where critical cell boundaries must be stabilized. Candidates include inflammatory joint disease, myocarditis, biliary atresia, and atherosclerosis.

In summary, we believe the ability of apoJ to bind hydrophobic domains may allow it to interact with a broad range of biological compounds. Its localized production by a variety of specialized cells lining fluid compartments in fetal and adult mice, and similar human tissues, suggests a fundamental and conserved role in maintaining many local environments. Its presence at cell surfaces and its ubiquitous presence in virtually all types of biological fluids may protect cell membranes exposed to deleterious components. Surface-active hydrophobic compounds and extracellular fluid phase compounds could be neutralized at or near the cell membrane by formation of soluble complexes. In this manner, apoJ may play a fundamental role in protecting cellular membranes exposed to potentially toxic hydrophobic moieties.

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1. Jordan-Starck, T. C., Witte, D. P., Aronow, B. J. & Harmony, J. A. K. (1992) *Curr. Opin. Lipidol.* **3**, 75–85.
2. Danik, M., Chabot, J.-G., Mercier, C., Benabid, A.-L., Chauvin, C., Quirion, R. & Suh, M. (1991) *Proc. Natl. Acad. Sci. USA* **88**, 8577–8581.
3. May, P. C., Lampert-Etchells, M., Johnson, S. A., Poirier, J., Masters, J. N. & Finch, C. E. (1990) *Neuron* **5**, 831–839.
4. Jenne, D. E. & Tschopp, J. (1989) *Proc. Natl. Acad. Sci. USA* **86**, 7123–7127.
5. Collard, M. W. & Griswold, M. D. (1987) *Biochemistry* **26**, 3297–3303.
6. Kirszbaum, L., Sharpe, J. A., Murphy, B., d'Apice, A. J. F., Classon, B., Hudson, P. & Walker, I. D. (1989) *EMBO J.* **8**, 711–718.
7. de Silva, H. V., Stuart, W. D., Park, Y. B., Mao, S. J. T., Busch, S. J., Gil, C. M. & Harmony, J. A. K. (1990) *J. Biol. Chem.* **265**, 14292–14297.
8. de Silva, H. V., Harmony, J. A. K., Stuart, W. D., Gil, C. M. & Robbins, J. (1990) *Biochemistry* **29**, 5380–5389.
9. Burkey, B. F., de Silva, H. V. & Harmony, J. A. K. (1991) *J. Lipid Res.* **32**, 1039–1048.
10. Urban, J., Parczyk, K., Leutz, A., Kayne, M. & Kondor-Koch, C. (1987) *J. Cell Biol.* **105**, 2735–2743.
11. Watts, M. J., Dankert, J. R. & Morgan, E. P. (1990) *Biochem. J.* **265**, 471–477.
12. de Silva, H. V., Stuart, W. D., Duvic, C. R., Wetterau, J. R., Ray, M. J., Ferguson, D. G., Albers, H. W., Smith, W. R. & Harmony, J. A. K. (1990) *J. Biol. Chem.* **265**, 13240–13247.
13. O'Bryan, M. K., Baker, H. W. G., Saunders, J. R., Kirszbaum, L., Walker, I. D., Hudson, P., Liu, D. Y., Glew, M. D., d'Apice, A. J. F. & Murphy, B. F. (1990) *J. Clin. Invest.* **85**, 1477–1486.
14. James, R. W., Hochstrasser, A.-C., Borghini, I., Martin, B., Pometta, D. & Hochstrasser, D. (1991) *Arterioscler. Thromb.* **11**, 645–652.
15. Jenne, D. E., Lowin, B., Peitsch, M. C., Bottcher, A., Schmitz, G. & Tschopp, J. (1991) *J. Biol. Chem.* **266**, 11030–11036.
16. Sylvester, S. R., Skinner, M. K. & Griswold, M. D. (1984) *Biol. Reprod.* **31**, 1087–1101.
17. Blaschuk, O. W., Burdzy, K. & Fritz, I. B. (1983) *J. Biol. Chem.* **258**, 7714–7720.
18. Morales, C. R. & Griswold, M. D. (1991) *Cell Tissue Res.* **263**, 125–130.
19. Sylvester, S. R., Morales, C., Oko, R. & Griswold, M. D. (1991) *Biol. Reprod.* **45**, 195–207.
20. Harding, M. A., Chadwick, L. J., Galtone, V. H., II, & Calvet, J. P. (1991) *Dev. Biol.* **146**, 483–490.
21. Hartmann, K., Rauch, J. R., Urban, J., Parczyk, K., Diel, P., Pilarksy, C., Appel, D., Haase, W., Mann, K., Weller, A. & Koch-Brandt, C. (1991) *J. Biol. Chem.* **266**, 9924–9931.
22. Witte, D. P., Wiginton, D. A., Hutton, J. J. & Aronow, B. J. (1991) *J. Cell Biol.* **115**, 179–190.
23. Watanabe, M. (1980) *J. Morphol.* **163**, 349–365.
24. Jenne, D. E. & Tschopp, J. (1992) *Trends Biochem. Sci.* **17**, 154–159.
25. Alpini, G., Lenzi, R., Zhai, W., Slott, P., Liu, M., Sarkozi, L. & Tavoloni, N. (1989) *Am. J. Physiol.* **257**, G124–G133.
26. Cohn, S. A. (1955) *J. Histochem. Cytochem.* **3**, 342–353.
27. Olcese, J. & Wesche, A. (1989) *Comp. Biochem. Physiol.* **93A**, 655–665.
28. Basbaum, C. B., Mann, J. K., Chow, A. W. & Finkbeiner, W. E. (1984) *Proc. Natl. Acad. Sci. USA* **81**, 4419–4423.
29. Palmer, D. J. & Christie, D. L. (1992) *J. Biol. Chem.* **267**, 19806–19812.
30. Antunes-Rodrigues, J., Ramalho, M. J., Reis, L. C., Menani, J. V., Turrin, M. Q. A., Gutkowska, J. & McCann, S. M. (1991) *Proc. Natl. Acad. Sci. USA* **88**, 2956–2960.
31. Genest, J. & Cantin, M. (1988) *Rev. Physiol. Biochem. Pharmacol.* **110**, 1–125.
32. Ouellette, M. & Brakier-Gingras, G. (1988) *Biochem. Biophys. Res. Commun.* **155**, 449–454.
33. Montpetit, M. L., Lawless, K. R. & Tenniswood, M. (1986) *The Prostate* **8**, 25–36.
34. Sawczuk, I. S., Hoke, G., Olsson, C. A., Connor, J. & Buttyan, R. (1989) *Kidney Int.* **35**, 1315–1319.
35. Kyprianou, N. & Isaacs, J. T. (1988) *Endocrinology* **122**, 552–562.
36. Bandyk, M. G., Sawczuk, I. S., Olsson, C. A., Katz, A. E. & Buttyan, R. (1990) *J. Urol.* **143**, 407–413.
37. Duguid, J. R., Bohmont, C. W., Liu, N. & Tourtellotte, W. W. (1989) *Proc. Natl. Acad. Sci. USA* **86**, 7260–7264.
38. McNeill, T. H., Masters, J. N. & Finch, C. E. (1991) *Exp. Neurol.* **111**, 140–144.
39. Garden, G. A., Bothwell, M. & Rubel, E. W. (1991) *J. Neurol.* **22**, 590–604.
40. Murphy, B. F., Kirszbaum, L., Walker, I. D. & d'Apice, A. J. F. (1988) *J. Clin. Invest.* **81**, 1858–1864.
41. Choi, N.-H., Mazda, T. & Tomita, M. (1989) *Mol. Immunol.* **26**, 835–840.
42. Wilson, M. R., Roeth, P. J. & Easterbrook-Smith, S. B. (1991) *Biochem. Biophys. Res. Commun.* **177**, 985–990.
43. Brooimans, R., Stegman, S., van Dorp, W., van derWoude, F., van Es, L. & Daha, M. (1990) *FASEB J.* **4**, 1871A (abstr.).
44. Morris, K., Colten, H. & Bing, D. (1978) *J. Exp. Med.* **148**, 1007–1019.
45. Colten, H., Gordon, J., Rapp, H. & Borsos, T. (1968) *J. Immunol.* **100**, 788–792.
46. Sundstrom, S. A., Komm, B. S., Yi, Z., Teuscher, C. & Lyttle, C. R. (1989) *J. Biol. Chem.* **246**, 16941–16947.
47. Witte, D. P., Welch, T. R. & Beischel, L. S. (1991) *Am. J. Pathol.* **139**, 717–724.
48. Meri, S., Waldmann, H. & Lachmann, P. J. (1991) *Lab. Invest.* **65**, 532–537.
49. Firestein, G. S., Paine, M. M. & Littman, B. H. (1991) *Arthritis Rheum.* **34**, 1094–1105.
50. D'Cruz, O. J., Haas, G. G., Jr., Wang, B. & DeBault, L. E. (1991) *J. Immunol.* **146**, 611–620.