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Ultrastructural Characteristics of Glomeruli in FGS/Kist Mice Showing High Proteinuria

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고단백뇨를 보이는 FGS/Kist 마우스 사구체의 미세구조

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요 약

본 연구는 고단백뇨를 보이는 신장질환모델마우스(FGS/Kist mouse)의 사구체에 대한 미세구조학적 변화를 관찰하고자 수행하였다. 전반적으로 사구체내의 모세혈관은 주변부의 혈관사이세포(mesangial cell) 부위의 확장으로 인하여 관강이 좁아져 있었으며 관강내에는 점액양 물질들이 흔히 관찰되었다. 또한 사구체바닥판(basal lamina)이 모세혈관 사이의 공간쪽으로 돌출되어져 있는 소견들도 볼 수 있었다. 혈관사이세포 부위에는 주변부와 뚜렷이 구분되는 전자밀도가 높은 물질들이 많이 차여져 있었다. 한편, 사구체바닥판에 인접하여 존재하고 있는 발세포들(podocytes)은 세포질내 많은 공포들이 관찰되었고, 발세포들이 내고 있는 발세포발(foot process)들은 서로 융합되거나 소실되어 매우 불규칙적인 소견을 보였다.

Key words : Ultrastructure, FGS, glomeruli

INTRODUCTION

Frequently, most renal diseases are accompanied with various morphological changes such as focal glomerular sclerosis (FGS), glomerular hypertrophy, dilatation of renal tubule and interstitial fibrosis, as well as clinical findings like proteinuria, hypoproteinemia and hypercholesterolemia (Floege *et al.*, 1995; Kohaut *et al.*, 1976; Metcoff *et al.*, 1951; Salant *et al.*, 1980; Vernier *et al.*, 1961). These morphological features are closely associated with the progression degree of renal injuries caused by many factors leading to disease conditions. Among the histopathological lesions, some terms have been used to describe the FGS, ranging from the simple term focal sclerosis to focal hyalinosis (Hori and Abrass, 1990; Kazatchkine *et al.*, 1982; Mauer *et al.*, 1981; Neale *et al.*, 1994; Sato *et al.*,

1987). At present, although the term for FGS is somewhat nonspecific and insufficient, it is used as the term for a lesion or a pattern that can occur concomitantly with the disease conditions of glomeruli as well as with other conditions of non-glomerular origin, and also is used as an important marker in the classification of idiopathic nephrotic syndrome (Demaine *et al.*, 1983; De Mouzon-Cambon *et al.*, 1981; Meroni *et al.*, 1990; Ruder *et al.*, 1983; Tejani *et al.*, 1983).

FGS is characterized by acellular, structureless material composed of glycoprotein and sometimes lipids in some glomeruli of patients with nephrotic syndrome in light microscpical studies. Moreover, the findings such as the effacement of foot processes, vacuolization of visceral epithelial cells and lamellation of basal lamina are also found by electron microscopy (Diamond *et al.*, 1992; Matsumoto and Atkins, 1989; Nakamura *et al.*, 1994; Saito *et al.*, 1993; Schwartz and Lewis, 1985). Many investigators have made numerous efforts to elucidate the mechanism of these findings, but the precise pathogenesis is still unclear.

Recently, Hyun *et al.* (1991) reported a new mouse strain as an animal model for human renal disease, and this mouse strain is considered as a very useful animal model for studying the mechanism of FGS. However, precise morphological characteristics have not been described sufficiently. Therefore, the present study was attempted to observe the ultrastructural characteristics of glomeruli in FGS/Kist mouse strain.

MATERIALS AND METHODS

1. Animals

Under the barrier system of air-conditioned room at 22±2°C, 55±5% relative humidity and 12 hrs L/D cycle of KRIBB, FGS/Kist mice (registered by "Kist") have been maintained by brother-sister mating Moreover, all animals were bred in the polycarbonate cages with free access to a pellet diet and water. As experimental group, 20 FGS/Kist mice showing three positive or more higher value of proteinuria in uropaper strip (Eiken Chemical, Japan) assessment were used. CBA/Kist mice were used as control group.

2. Electron microscopy

The kidneys were minced at 1~2 mm square, fixed immediately in 2.5% glutaraldehyde in 0.05 M cacodylate buffer for 4 hours, followed by postfixation in 1% osmium tetroxide; tissue was dehydrated in the graded concentrations of ethanol and embedded in Epon 812. The thin sections were stained with lead citrate and uranyl acetate, and examined by electron microscope (Hitachi 600A, Japan).

RESULTS

1. Control group

As control group, the glomeruli of CBA/Kist mice didn't show the significant changes in the electron microscopical observation. That is, endothelial, mesangial and visceral epithelial cells as well as the regions of capillary wall performing the role of filtration barrier in the glomeruli were intact. These findings were shown in Fig. 1 and 2.

2. Experimental group

The glomeruli of FGS/Kist mice showed the findings such as mucus-like substance in capillary lumen of glomeruli (Fig. 3), projection of basal lamina (Figs. 4, 5), vacuolization of podocyte (Fig. 6), electron-dense deposits of mesan-

gial area (Fig. 7), narrowness of capillary lumen (Fig. 8), widening of mesangial area (Fig. 9), attachment of Bowman's capsule (Fig. 10) and sclerotic changes accompanied with the irregular-shaped foot process fusion or the effacement of podocytes in areas adjacent to basal lamina of glomeruli (Figs. 11-13).

DISCUSSION

Focal glomerular sclerosis (FGS) has usually been used to describe the light microscopic process involving the diffuse and somewhat generalized effacement of glomerular visceral epithelial cell foot processes (Floege *et al.*, 1995; Kohaut *et al.*, 1976; Metcoff *et al.*, 1951; Salant *et al.*, 1980; Vernier *et al.*, 1961). Ultrastructurally, FGS appears the findings such as the deposits of electron-dense substance in the mesangial area and the vacuolization of visceral epithelial cells (Hayslett, 1979; Koyoku *et al.*, 1981; Theofilopoulos and Dixon, 1985). Actually, these findings have been described in patients afflicted with renal disease and experimental animal model by many investigators (Azar *et al.*, 1977; Grond *et al.*, 1982; Still and Dennison, 1969). Moreover, as causative factors of FGS, the hemodynamic, immunological, genetical and metabolic factors are known to be involved (Albini *et al.*, 1985; Andreoli *et al.*, 1986; Nagy *et al.*, 1981).

At present study, the glomeruli of control group were observed as having normal structures, while FGS/Kist mice appeared the findings such as widening of mesangial area, electron-dense deposits of mesangial area and effacement or fusion of foot processes in visceral epithelial cells. These findings were considered to be suggesting the existence of severe damages within the glomeruli of FGS/Kist mouse strain. Perhaps it seems to be resulted from the persistent protein uria in FGS/Kist mouse strain. Some investigators (Miller *et al.*, 1990; Nath *et al.*, 1992; Savin, 1993) described that proteinuria is usually related with the various lesions of glomeruli including capillary walls, swelling and hypertrophy of visceral epithelial cells, extensive fusion or effacement of foot processes and hyaline granular changes. Moreover, other investigators (Hayslett, 1979; Koyoku *et al.*, 1981; Theofilopoulos and Dixon, 1985; Azar *et al.*, 1977; Grond *et al.*, 1982; Still and Dennison, 1969; Albini *et al.*, 1985; Andreoli *et al.*, 1986; Nagy *et al.*, 1981) reported that the similar ultrastructural changes had been observed in their experiments of human or experimental renal disease.

On the basis of above described, FGS/Kist mouse strain is considered to be having the ultrastructural similarites with FGS of human or induced renal disease. Therefore, if further studies are done, it seems that the FGS/Kist mouse strain could play a pathophysiologically important role in elucidating the mechanism of FGS.

ABSTRACT

Using the electron microscopical method, this study was attempted to investigate the ultrastructural characteristics of glomeruli in FGS/Kist mice showing high proteinuria. The mucus-like substances were observed in glomerular capillary lumen which were usually narrowed by the widening of mesangial area filled with electron-dense deposits. Some portions of basal lamina in capillary wall were projecting to urinary space. Moreover, many vacuoles were observed in the cytoplasm of visceral epithelial cells, and an irregular-shaped fusion or effac-

ment of foot processes were often shown in areas adjacent to basal lamina of glomeruli.

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FIGURE LEGENDS

Fig. 1. Electron micrograph of CBA/Kist mice showing the normal mesangial cells (M), endothelial cell (E), podocytes (P) and capillary lumen (*). Bar=6.33 μm.

Fig. 2. More higher findings of renal glomerulus showing the well-defined foot processes (large arrows), filtration slits (small arrows) and primary process (arrow head) in CBA/Kist mice. *: Capillary lumen, M: Mesangial cells, P: Podocytes, Bar=1 μm.

Fig. 3. Electron micrograph of FGS/Kist mice showing the foot process fusion and mucus-like substances in the capillary lumen. *: Capillary lumen. Bar=2.33 μm.

Fig. 4. Electron micrograph of FGS/Kist mice showing the basal lamina projections (arrows) toward urinary space. *: Capillary lumen, M: Mesangial cells, Bar=2.33 μm.

Fig. 5. Electron micrograph showing the basal lamina projection (arrow) and mucus-like substances in the capillary lumen of FGS/Kist mice. *: Capillary lumen, Bar=2.33 μm.

Fig. 6. Electron micrograph showing the vacuolization of podocyte (stars) in FGS/Kist mice. *: Capillary lumen, Bar=2.33 μm.

Fig. 7. Electron micrograph of FGS/Kist mice showing the electron-dense deposits (arrows) in the mesangial area. *: Capillary lumen, M: Mesangial cells, P: Podocyte, Bar=2.33 μm.

Fig. 8. Electron micrograph of FGS/Kist mice showing the electron-dense deposits (stars) in the mesangial area and the narrowness of capillary lumen (*). M: Mesangial cells, Bar=2.33 μm.

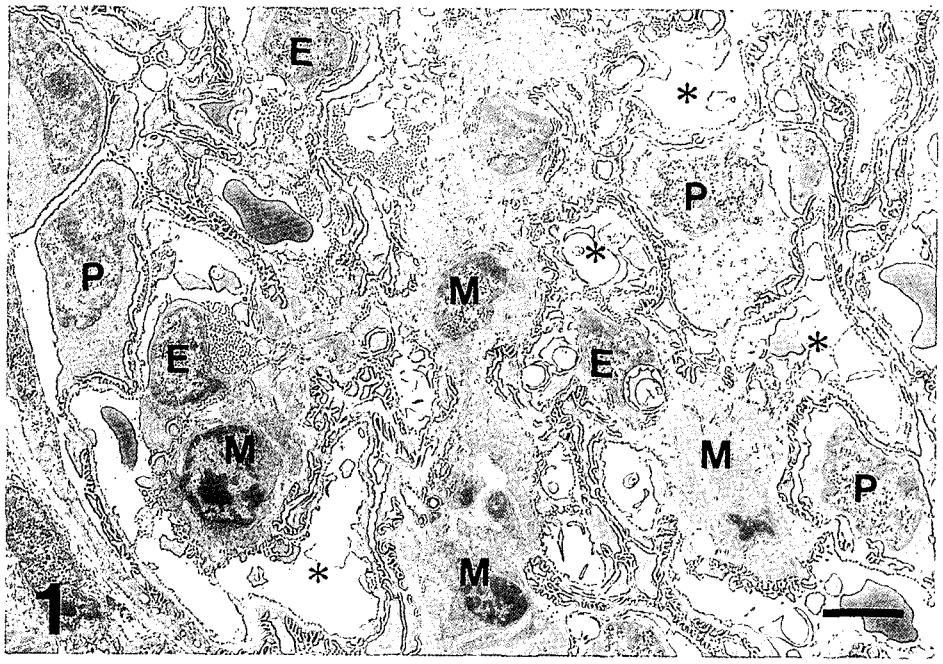
Fig. 9. Electron micrograph of FGS/Kist mice showing the sclerotic changes in mesangial area and the foot-process fusion of podocyte. P: Podocytes, Bar=2.33 μm.

Fig. 10. Electron micrograph of FGS/Kist mice showing the sclerotic change and the attachment of Bowman's capsule. M: Mesangial cell, P: Podocyte, TC: Tubular cell, Bar=2.33 μm.

Fig. 11. Electron micrograph of FGS/Kist mice showing the severe sclerotic change in the mesangial area (MA). M: Mesangial cell, Bar=3.50 μm.

Fig. 12. Electron micrograph of FGS/Kist mice showing the severe sclerotic changes in mesangial area (MA) and the foot-process fusion of podocyte (arrows). M: mesangial cell, *: Capillary lumen, Bar=3.50 μm.

Fig. 13. Another electron micrograph of FGS/Kist mice showing the severe sclerotic changes in mesangial area (MA) containing the electron-dense deposit (stars) and the foot-process fusion of podocyte (arrows). Bar=3.50 μm.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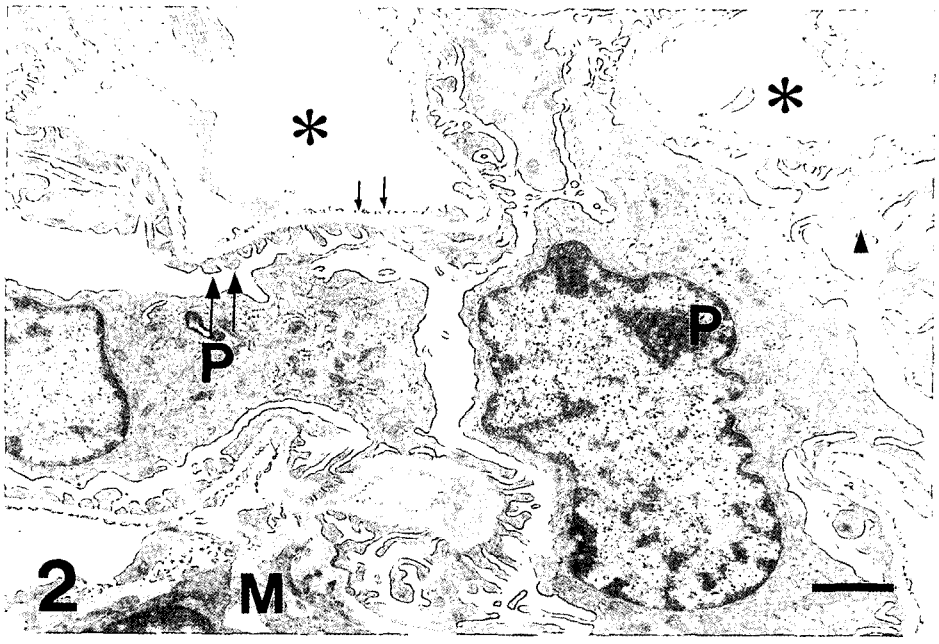
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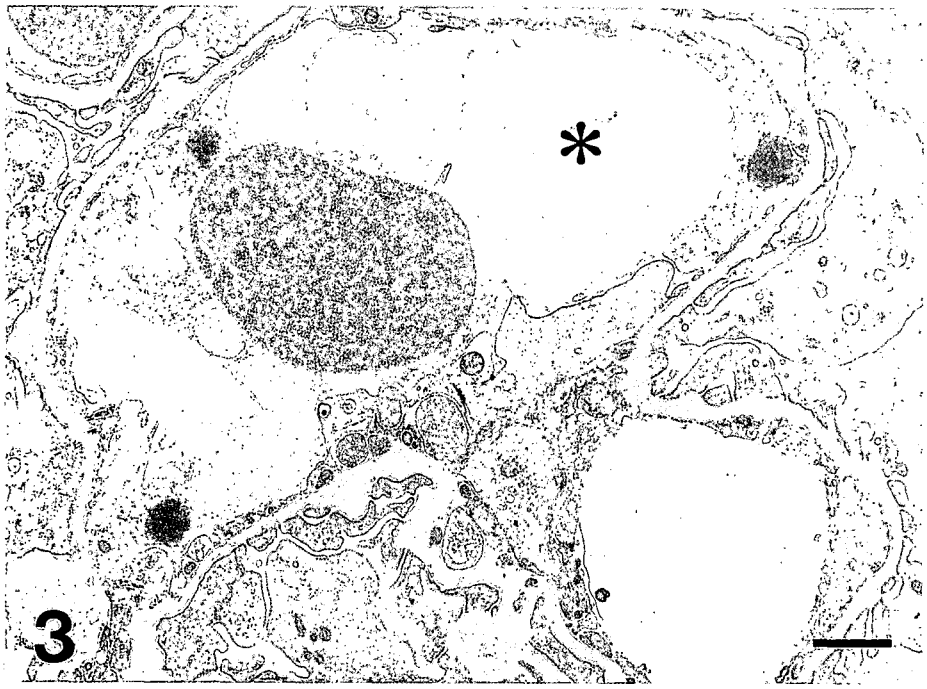
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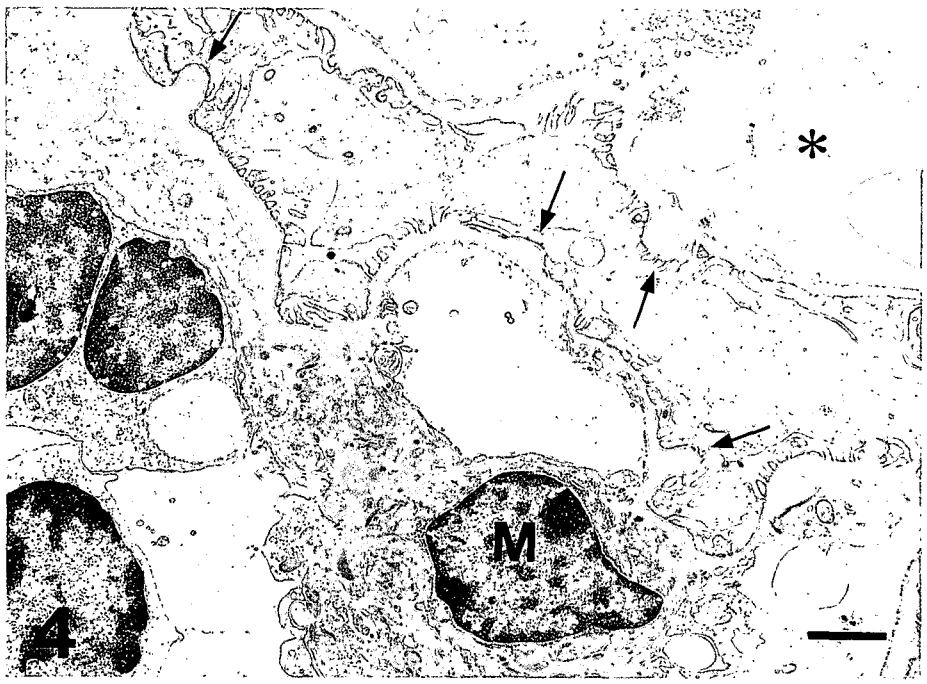
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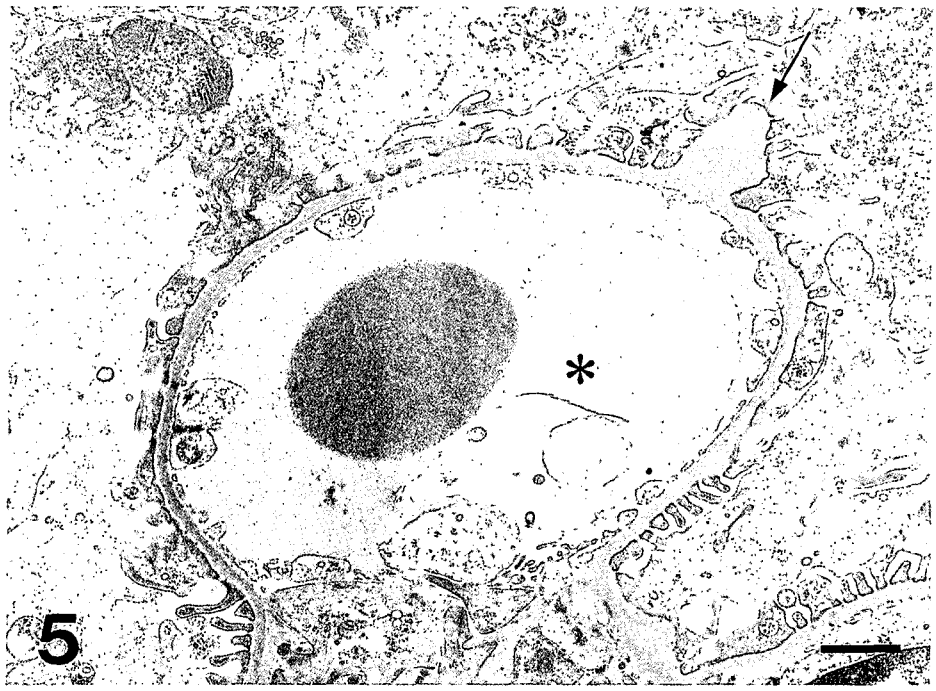
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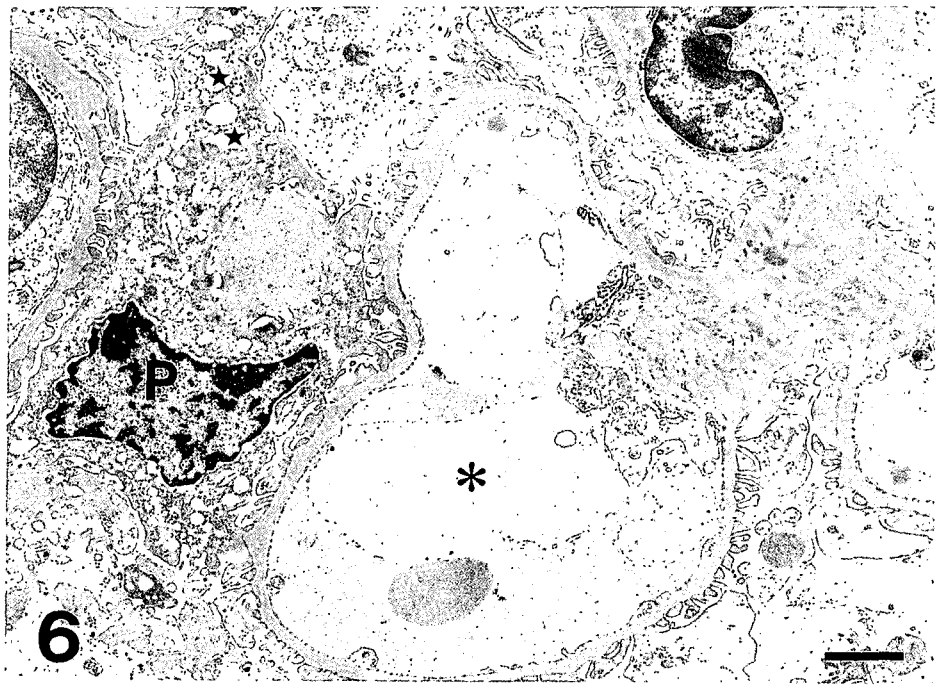
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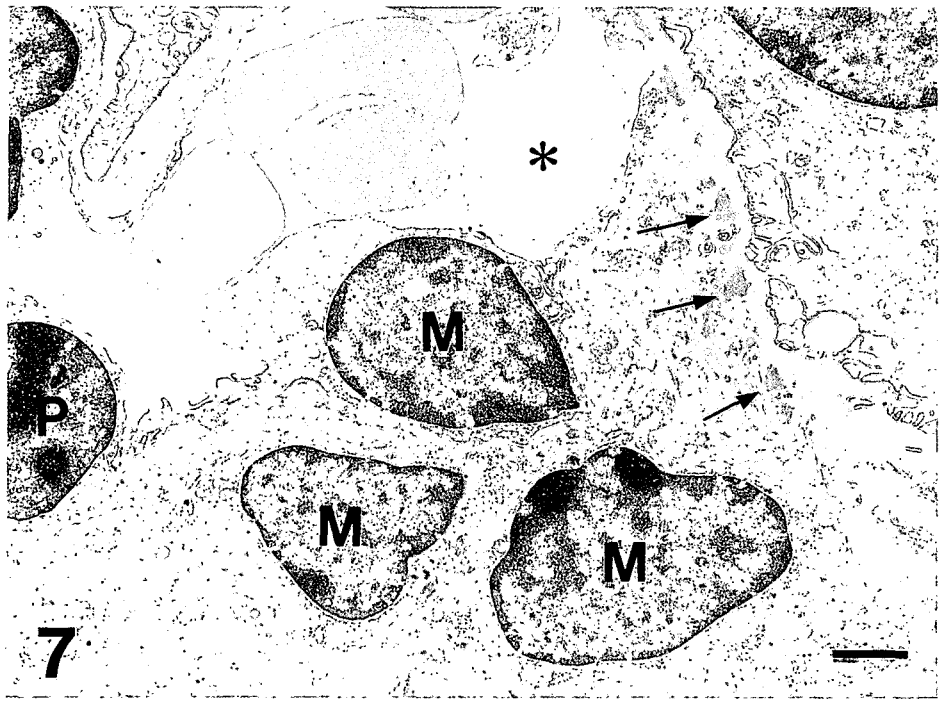
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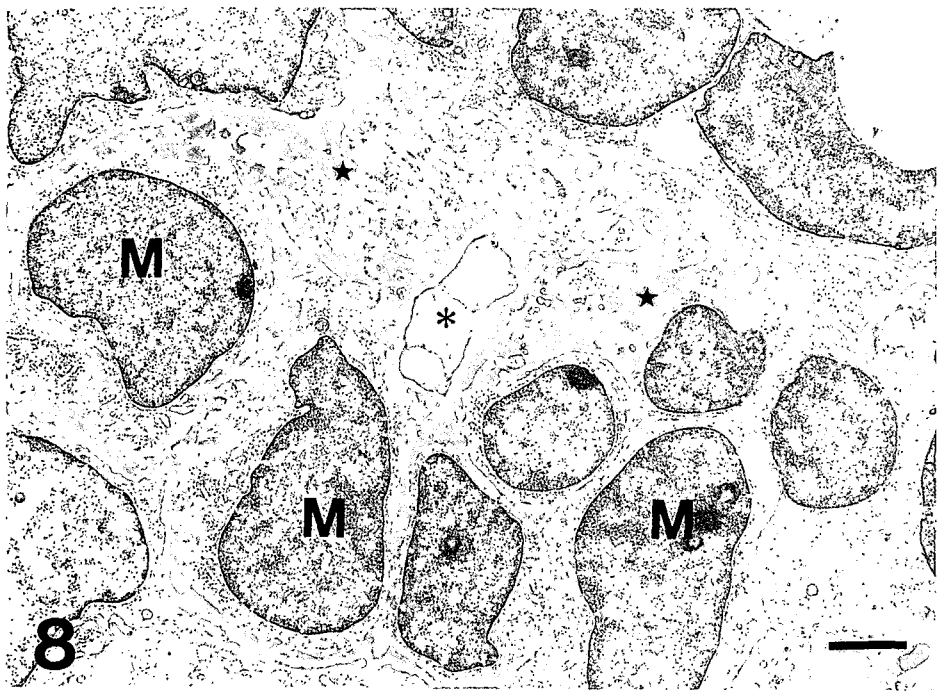
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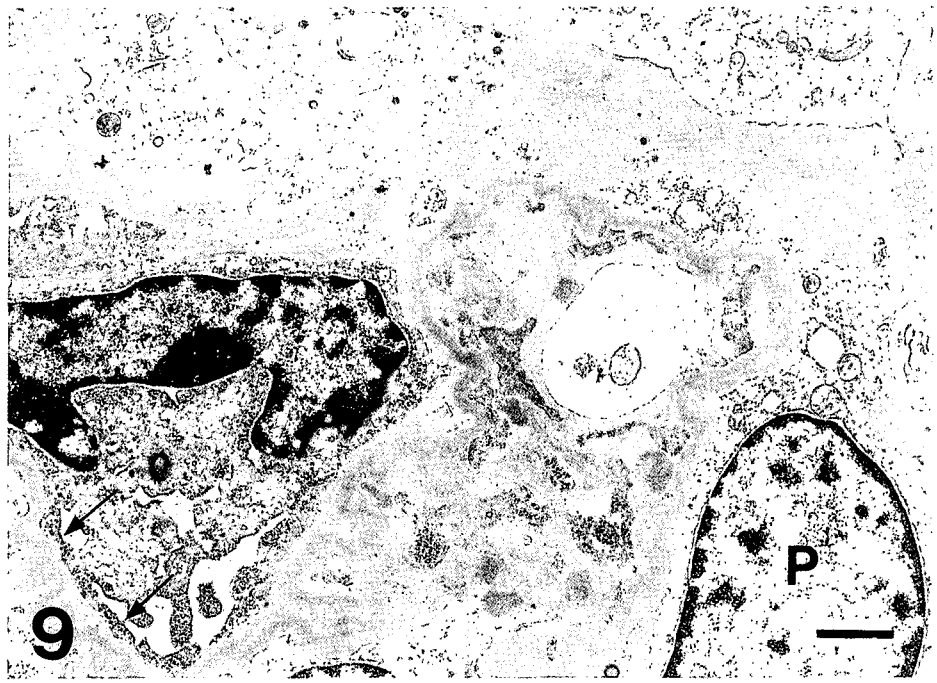
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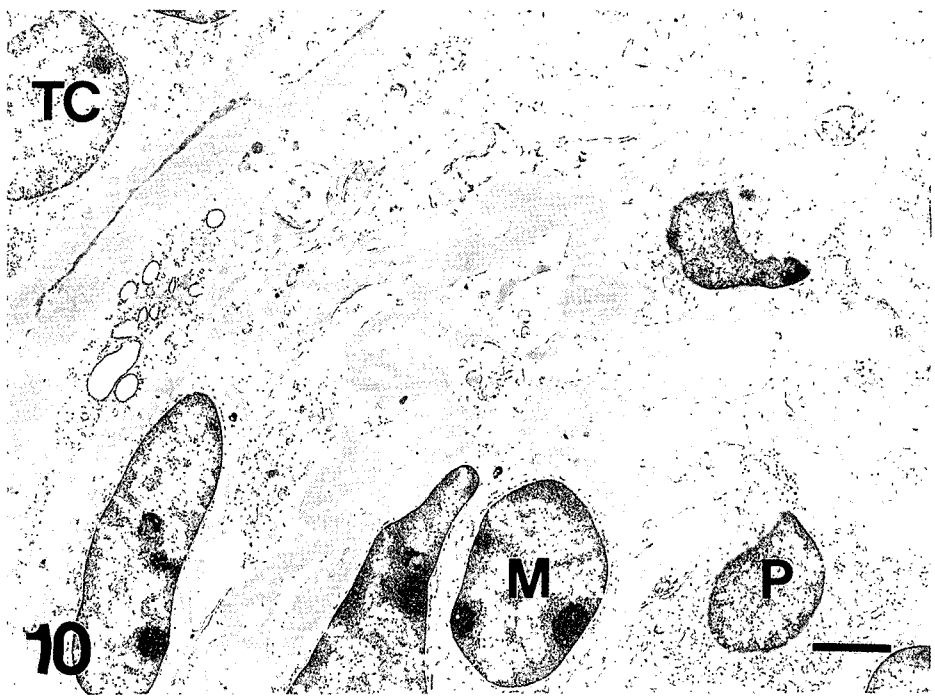
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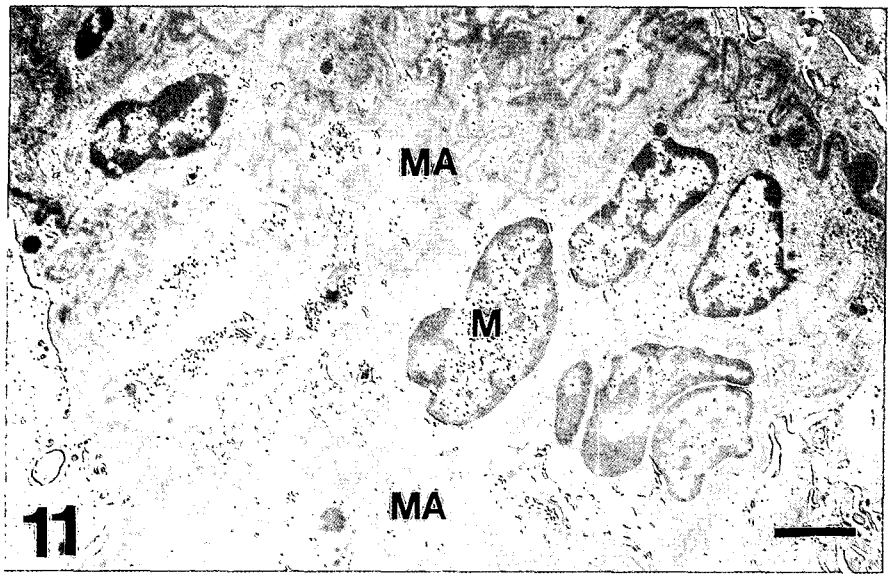
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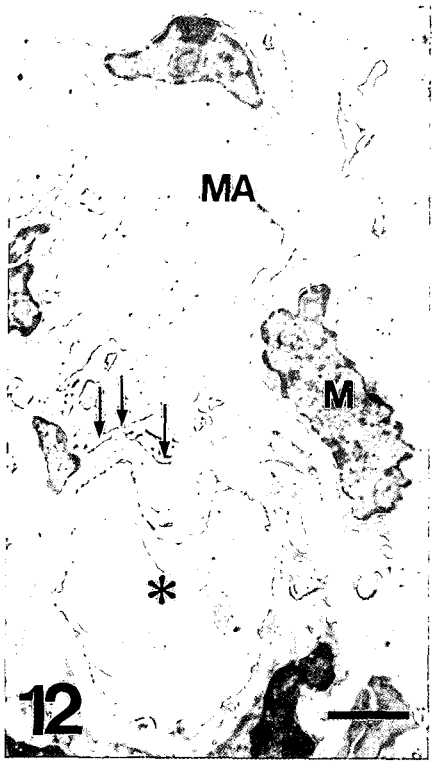
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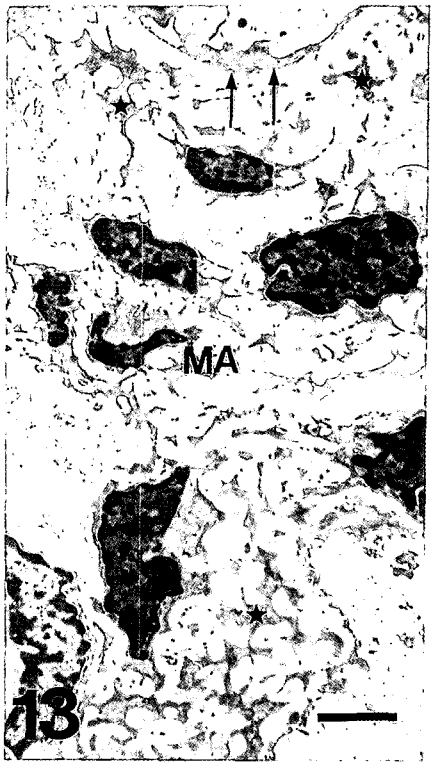
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