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Glomerular Changes in Rats Administered ABT-869, a Multitargeted Receptor Tyrosine Kinase Inhibitor - Linking Ultrastructure to Mechanism

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ABT-869, a multitargeted receptor tyrosine kinase inhibitor in development as an anti-cancer agent, blocks VEGF and PDFG signaling pathways, which are required by endothelial cells for survival[1]. Thus one of the mechanisms whereby ABT-869 exerts antitumor effects is by inhibiting tumor blood vessel growth. However, normal blood vessels, such as those in glomeruli, also require VEGF for maintenance [2]. In addition, glomerular epithelial cells (podocytes) express high levels of VEGF, and disruption of VEGF signaling in rats and mice has been shown to damage both glomerular endothelial cells and podocytes, resulting in proteinuria [3]. In this study, administration of ABT-869 to rats resulted in ultrastructural changes in glomerular endothelial cells and podocytes consistent with the mechanism of action, i.e., inhibition of VEGF signaling.

ABT-869 was administered orally to female rats for two weeks, followed by a two-week dose-free recovery period. By transmission electron microscopy, there were ultrastructural changes in glomeruli of rats administered ABT-869 (Figure 1). Endothelial cells had increased numbers of irregular luminal cytoplasmic processes; fenestration of endothelial cells in capillary loops was reduced; and there were subendothelial, electron dense deposits in glomerular basement membranes.

Podocytes from dosed rats also exhibited alterations, particularly in filtration elements, i.e., decreased numbers of foot processes and filtration slits. In addition, podocytes (and mesangial cells) contained large numbers of electron-dense granules that were likely protein absorbed from urine. A few podocytes appeared damaged, with vacuolization and increased electron-density.

The functional correlate of these changes was an increase in urine protein at the end of the dosing period. However, two-weeks after the last dose was administered, proteinuria and most ultrastructural changes had resolved in nearly all rats. Persistence of both proteinuria and glomerular ultrastructural changes in one rat at the end of the recovery period further supports the direct link between ultrastructure and function.

The ultrastructural changes and resultant proteinuria seen in this study are consistent with the mechanism of action of ABT-869 and can be considered exaggerated pharmacological responses. In human patients administered currently marketed VEGF inhibitors, proteinuria has proven to be readily monitorable and reversible upon discontinuation of therapy [4].

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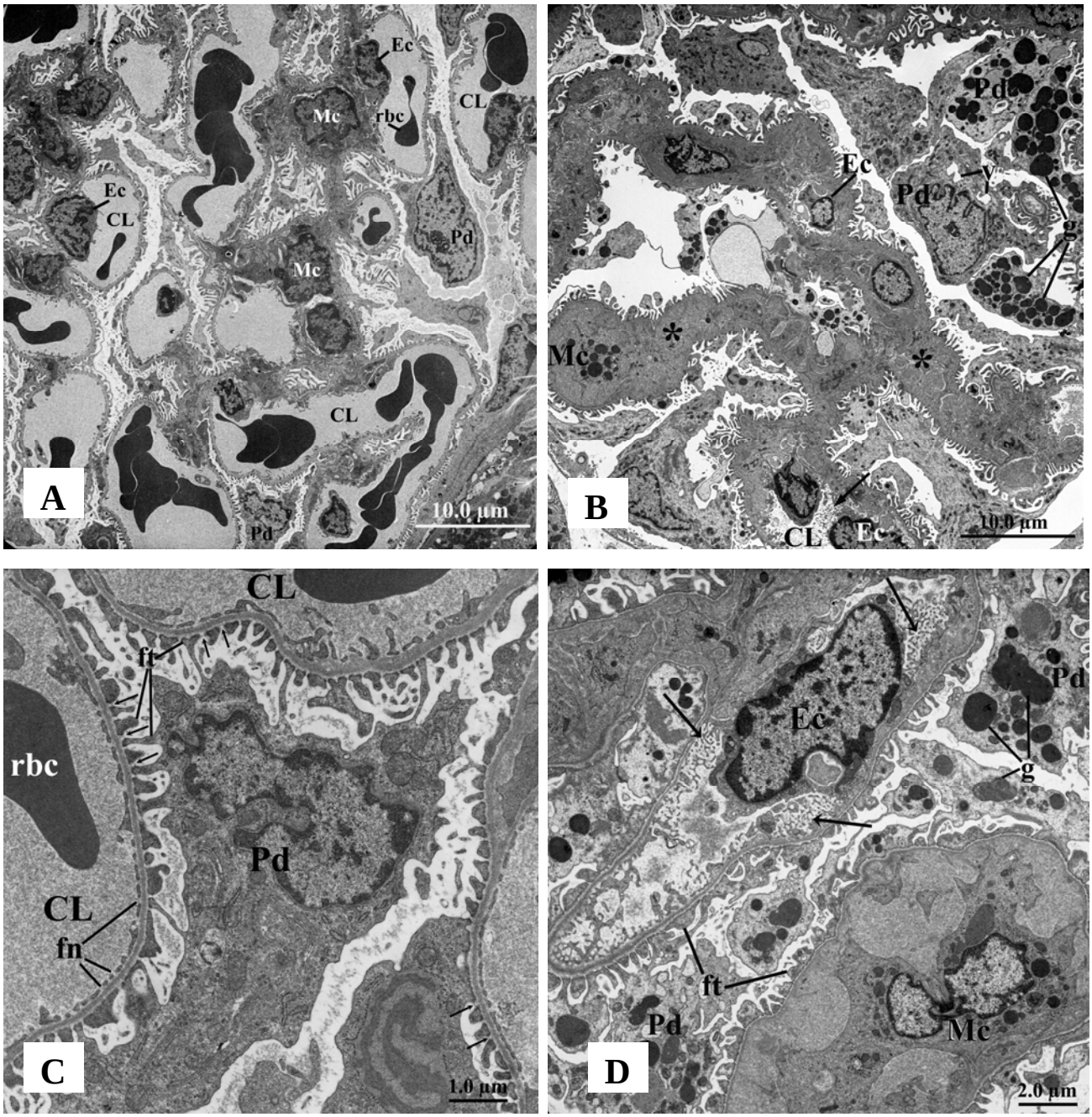

Figure 1. Ultrastructural changes in renal glomeruli. A and C, control rats; B and D, ABT-869 dosed rats. Endothelial cell (Ec); erythrocyte (rbc); capillary lumen (CL); endothelial cell fenestrations (fn); cytoplasmic processes of Ec (arrows). Podocyte (Pd); granules in podocytes (g); podocyte foot processes (ft); mesangial cell (Mc), mesangial matrix (*).

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