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Response

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In reply: We thank Dr Pan *et al* for your interest in our article.[1] Our finding that KIT is expressed on the cell membrane of chromophobe renal cell carcinomas (RCCs) corresponds with other recent reports.[2–6] However, there are some controversies on the expression of KIT in normal renal tubular cells and papillary RCCs.[1–6] In contrast to our paper,[1] Dr Pan *et al* proposed that KIT expression in the cytoplasm of normal renal tubular cells and papillary RCCs is due to a technical difference by using EDTA as HIER buffer. In addition, Dr Pan *et al* suggested that the immunoreactive KIT in the cytoplasm of normal tubular cell and papillary RCC might be an unknown protein with a structural similarity or cross-reactivity with anti-KIT antibody (DAKO, Carpinteria, CA, USA).[2]

First, we would like to mention in more detail about the expression of KIT in the normal renal tubular cells.[1] In fact, KIT was expressed in the cytoplasm of the cortical distal tubules while it was expressed in the cell membrane and cytoplasm of the intercalated cells of the cortical collecting ducts. Interestingly, the membranous immunoreactivity of KIT was enhanced in the basal side of cell membrane of the intercalated cells (Figure 1a and b). Papillary and chromophobe RCCs are thought to arise from the cortical distal tubular cells and intercalated cells of the cortical collecting ducts, respectively.[7] Surprisingly, the expression patterns of KIT between normal tubular cells and RCCs are very similar in view of the histogenesis of RCCs.

To address the heat-induced epitope retrieval (HIER) issue raised by Dr Pan *et al*, we again compared the effects of EDTA and citrate buffer. However, we obtained the same results of immunohistochemical staining, regardless of using the different HIER buffers (Figure 1). It is also expected in part by the fact that both EDTA and citrate buffers have the same function of calcium-chelating ability during HIER, although their potencies are rather different.[8] Thus, it is evident that HIER buffer does not affect the immunoreactivity for KIT. Furthermore, Dr Pan *et al* suggested that cytoplasmic immunostaining for KIT is probably nonspecific due to nonspecific adsorption or cross-reactivity for some unknown mitochondrial proteins.[2] However, we think that it is rather self-contradictory because KIT expression is strongly membranous in the eosinophilic variant of chromophobe RCCs and oncocytomas, despite having abundant mitochondria in their cytoplasms.[1–6]

We also found that KIT is expressed in 9 of 10 cases of sarcomatoid RCC (90%) in the same experimental condition except an antibody dilution of 1:100. KIT was expressed only in the cytoplasm of high-grade pleomorphic sarcoma cells. The result is in agreement with other reports.[6,9] The KIT expression in sarcomatoid RCCs was cytoplasmic as the same as that of papillary RCCs. In our experience, their expressions for KIT were rather lower than those of chromophobe RCCs and oncocytomas. As Dr Pan *et al* indicated, we did immunohistochemistry for KIT in the limited cases of papillary urothelial carcinomas in the renal pelvis. In our paper,[1] we focused more on the therapeutic implication of KIT expression rather than diagnostic one in RCCs. It is noteworthy that concurrent papillary RCC and gastrointestinal stromal tumor are reported, suggesting a unique molecular association between these tumors.[10] However, we certainly agree with Dr Pan *et al* that further studies using fresh tissue samples or cancer cell lines are needed to clarify the issues.

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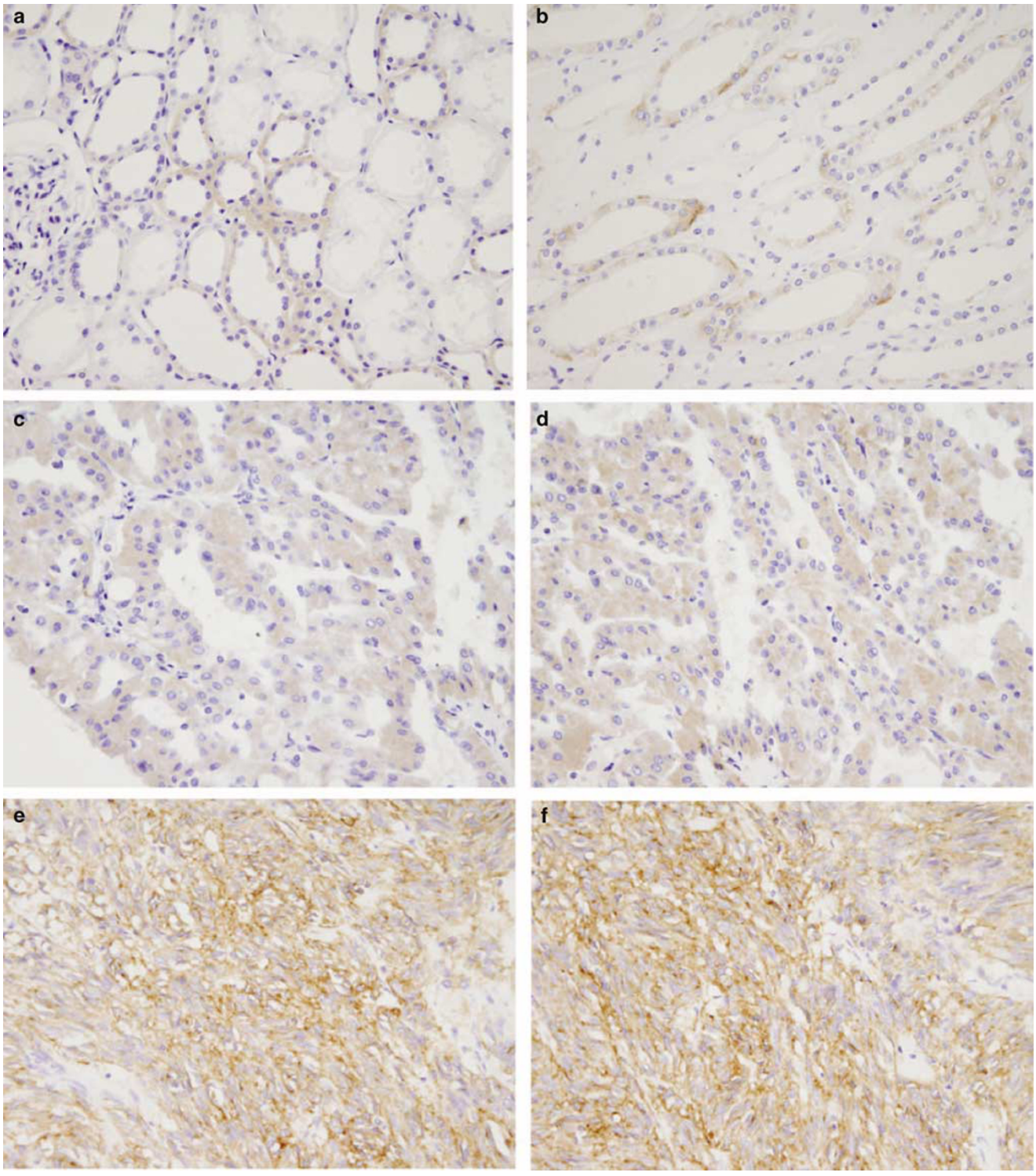

Figure 1 Immunohistochemistry for KIT. (**a**) KIT was expressed in the cytoplasm of the cortical distal tubular cells (HIER with citrate buffer, antibody dilution; 1:100). (**b**) KIT was expressed in the basal side of membrane and cytoplasm of the intercalated cells of the cortical collecting ducts (HIER with citrate buffer, antibody dilution; 1:100). (**c**) and (**d**) KIT was expressed in the cytoplasm of papillary renal cell carcinoma (HIER with 10 mM citrate buffer, pH 6.0 and 1 mM EDTA, pH 8.0, antibody dilution; 1:100, respectively). (**e**) and (**f**) KIT was expressed in the cytoplasm of gastrointestinal tumor (HIER with 10 mM citrate buffer, pH 6.0 and 1 mM EDTA, pH 8.0, antibody dilution; 1:100, respectively) (immunoperoxidase, $\times$ 400 magnification).

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