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Vitamin D inhibition of TACE and prevention of renal osteodystrophy and cardiovascular mortality☆

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ABSTRACT

In the course of kidney disease, the progressive loss of renal capacity to maintain normal serum levels of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) is a main contributor to parathyroid hyperplasia and high serum PTH. High PTH causes mineral and skeletal abnormalities predisposing to ectopic calcifications and increased mortality. Intriguingly, replacement therapy with $1,25(OH)_2D$ or its less calcemic analogs was recently shown to improve survival in kidney disease patients through renal and cardiovascular protective actions that are independent of PTH suppression. This work presents preliminary evidence that $1,25(OH)_2D$ inhibition of TACE (Tumor necrosis factor Alpha Converting Enzyme) is a potential common mechanism underlying the efficacy of therapy with $1,25(OH)_2D$ or its analogs to improve outcomes in chronic kidney disease. $1,25(OH)_2D$ prevents/moderates not only the onset and progression of parathyroid TACE/TGFα-driven secondary hyperparathyroidism, but, more significantly, renal TACE/TGFα-driven fibrotic and inflammatory lesions to the renal parenchyma, and TACE/TNFα-driven systemic inflammation, which is known to aggravate renal and cardiovascular lesions and enhance the risk of vascular calcification and cardiovascular mortality.

1. Introduction

In chronic kidney disease (CKD), disturbances in mineral and bone metabolism are prevalent, and an important cause of morbidity, decreased quality of life, and extraskeletal calcifications that have been associated with increased cardiovascular mortality [1]. The progressive loss of renal capacity to maintain normal serum levels of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the hormonal form of vitamin D, is a main contributor to the development of secondary hyperparathyroidism (SH). This disorder is characterized by parathyroid hyperplasia and high serum PTH. The elevations in serum PTH cause mineral and skeletal abnormalities predisposing to renal and cardiovascular damage, ectopic calcifications, and increased mortality. Because $1,25(OH)_2D$ suppresses parathyroid cell growth and PTH gene transcription, treatment with $1,25(OH)_2D$ or its less calcemic analogs has been the therapy of choice for SH for the last 25 years [1]. At present, the importance of correcting the abnormalities in vitamin D metabolism in CKD is being investigated vigorously in view of observational studies in hemodialysis patients suggesting a potential survival benefit of $1,25(OH)_2D$ replacement therapy. Intriguingly, the improved outcomes upon treatment with active vitamin D metabolites ($1,25(OH)_2D$ or its less calcemic analogs) involve renal and cardiovascular protective actions that are unrelated to their efficacy to suppress PTH [2]. Thus, a major challenge for nephrologists is the identification of the mechanisms underlying $1,25(OH)_2D$ efficacy to improve outcomes in CKD patients in a PTH-independent manner. This review presents preliminary evidence of $1,25(OH)_2D$ inhibition of TACE (Tumor necrosis factor Alpha Converting Enzyme, also known as ADAM17) as a potential mediator of $1,25(OH)_2D$ pro-survival properties in experimental CKD.

2. Increases in parathyroid TACE contribute to the onset and progression of SH

In advanced kidney disease, the severity of parathyroid hyperplasia determines not only a higher risk for cardiovascular mortality, but also a reduction in parathyroid levels of the vitamin D receptor (VDR) that makes these patients refractory to therapy with $1,25(OH)_2D$ or its analogs [1]. Our laboratory has identified the molecular link between the severity of parathyroid growth and VDR reduction: In rat and human SH, enhanced parathyroid expression of the potent growth promoter transforming growth factor-α (TGFα) and TGFα self-induction are sufficient to generate a feed-forward loop for TGFα activation of its receptor, the

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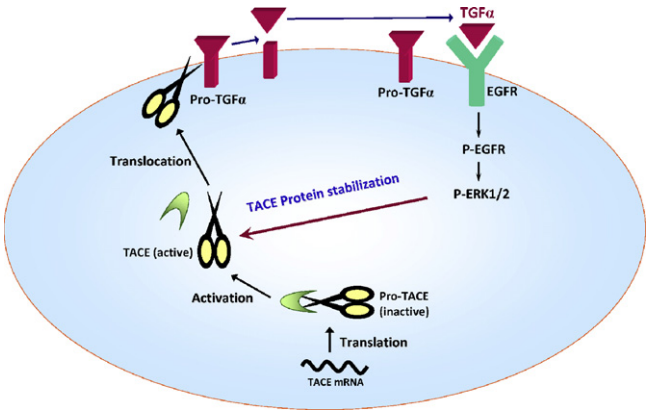

Fig. 1. Regulation of TACE expression and activity. Transcriptional and post-transcriptional mechanisms regulate cytosolic TACE content, its activation, stabilization, and translocation to the cell surface for its sheddase activity (see text for details).

EGFR, which aggravates growth and reduces VDR [3,4]. In fact, halting this loop with the use of highly specific EGFR-tyrosine kinase inhibitors not only prevents further increases in parathyroid TGFα levels and growth rates, but also prevents VDR reduction, hence restoring the response to vitamin D therapy. Thus, the identification of the molecule(s) that causes the initial increases in parathyroid TGFα and starts the vicious cycle for disease progression is critical to improve outcomes. To this end, we focused on TACE (ADAM17), a metalloproteinase essential for EGFR signaling, as it releases the mature isoforms of TGFα and several other EGFR-activating ligands thereby enhancing autocrine/paracrine EGFR activation [5,6]. Enhanced TACE expression associates directly with the severity of several TGFα driven hyperproliferative disorders that range from the induction of renal cystogenesis in polycystic kidney disease [7] to tumor progression in breast, colon, hepatocellular, renal and skin cancer [8,9]. In spite of the efficacy of TACE inhibition in attenuating these severe hyperproliferative disorders, the regulation of TACE expression remains poorly characterized. Transcriptional [10] and, most commonly, post-transcriptional regulation [11] deter-

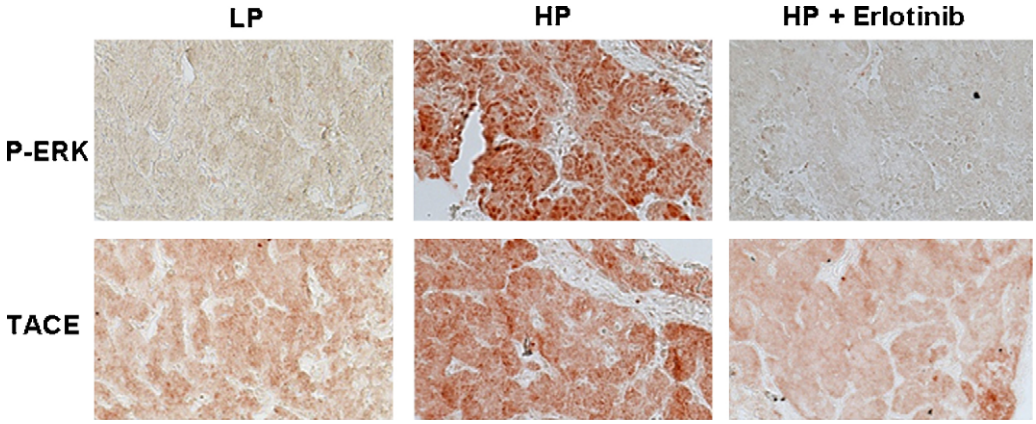

Fig. 2. Dietary P intake regulates parathyroid TACE expression. Representative immunostaining of phosphorylated ERK1/2 (P-ERK1/2) and TACE, in parathyroid glands from 5/6 NX rats fed either a low (0.2%) or a high (1.2%) P diet, and receiving vehicle or Erlotinib (6 mg/kg body weight), daily, for 1 week.

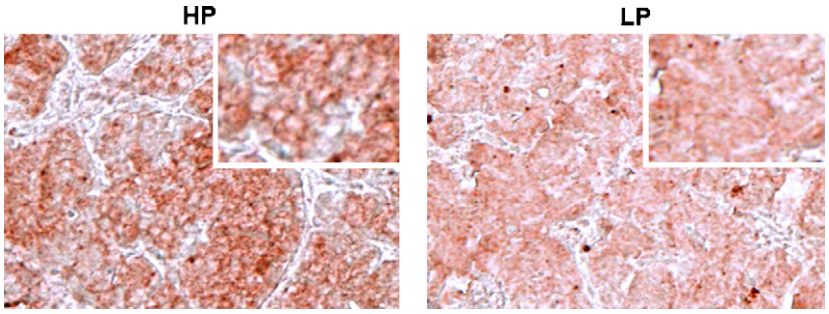

Fig. 3. Dietary P intake regulates parathyroid TACE translocation to the cell membrane. Representative immunostaining of TACE content at week 4, in parathyroid glands from 5/6 NX rats fed either a high P diet (0.9% P) for 4 weeks (HP), or for the first 2 weeks followed by a switch to a low P diet (0.2%) for 2 additional weeks (LP). The inserts show the higher TACE localization at the cell membrane in the HP group.

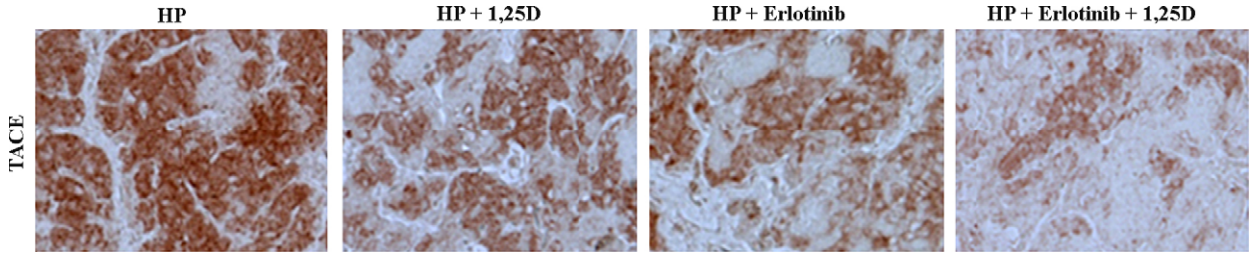

Fig. 4. 1,25$(OH)_2$D synergizes with Erlotinib in moderating the increases in parathyroid TACE content in rat SH. Representative immuno staining for parathyroid TACE in glands from 5/6 NX rats fed high P diet and receiving either vehicle or 1,25$(OH)_2$D (1,25D; 4 ng every other day), Erlotinib (6 mg/kg body weight) and combined Erlotinib + 1,25D treatment.

mine TACE levels and activity, as summarized in Fig. 1. Briefly, upon TACE synthesis, the removal of a domain of TACE that inhibits its catalytic activity at the late Golgi compartment is a critical prerequisite for TACE maturation as it progresses through the secretory pathway to the cell surface [12]. TACE location at the cell membrane is mandatory for its sheddase function, and its inhibition effectively impairs TACE activity [13]. Post-transcriptional mechanisms that increase TACE activity in EGFR-driven cancer include the induction of TACE protein stabilization by the activated-EGFR [11], and TACE phosphorylation by activated ERK- or fibroblast growth factor receptor, which enhances TACE progression along the secretory pathway to the plasma membrane [14]. From these reports and our demonstration of the key role of TGFα in the parathyroid hyperplasia of kidney disease, we examined whether elevations in parathyroid TACE contribute to the TGFα-driven vicious cycle of exacerbated growth and VDR reduction. Preliminary studies in the rat model of CKD have shown that high dietary phosphate (P), a well known inducer of parathyroid TGFα expression and growth rates, also enhances parathyroid TACE content in early and established SH (see Figs. 2 and 3). However, high dietary P may not affect parathyroid TACE expression directly, but induce its translocation to the cell surface for the release of TGFα required to initiate EGFR-driven parathyroid cell growth and TACE stabilization. In fact, the inhibition of TGFα/EGFR-signals with the administration of Erlotinib, a potent and highly specific inhibitor of EGFR activation, markedly attenuates high P-induction of parathyroid TACE content in early (see Fig. 2) and established (see Fig. 4) rat SH. Similarly, the prevention of TACE translocation to the cell surface to release TGFα appears to mediate the attenuation of parathyroid gland growth by dietary P restriction within the first week after 5/6 nephrectomy (NX) (see Fig. 2), as well as the halting of further parathyroid gland enlargement observed with the switch from a high to a low P diet from week 2 to week 4 after 5/6 NX (Fig. 3).

More significantly, $1,25(OH)_2D$ inhibition of parathyroid TACE contributes to suppress parathyroid cell growth. $1,25(OH)_2D$ could downregulate TACE simply by inhibiting its stabilization by activated-EGFR, as $1,25(OH)_2D$ potently inhibits EGFR activation [15]. To test this possibility, we compared the relative potency of the combination of $1,25(OH)_2D$ (4 ng thrice weekly) + Erlotinib (6 mg/kg bw daily) from week 2 to week 4 after 5/6 NX with that of either monotherapy to moderate the elevations in parathyroid TACE expression induced by high dietary P, in our rat model of established SH. Fig. 4 shows the higher efficacy of the Erlotinib + $1,25(OH)_2D$ combination to reduce parathyroid TACE content and, consequently, TACE-driven parathyroid gland enlargement (not shown) compared to that of either Erlotinib or $1,25(OH)_2D$, which suggests that $1,25(OH)_2D$ inhibits parathyroid TACE expression in an EGFR-independent manner. Computer analysis of the TACE gene promoter showed no vitamin D responsive elements and several C/EBP binding sites. Therefore, $1,25(OH)_2D$ suppression of parathyroid TACE expression could involve either VDR binding at distal VDREs in the TACE gene, or $1,25(OH)_2D$ induction of parathyroid C/EBPβ expression, as shown in renal cells and macrophages [16,17], and C/EBPβ transcriptional activity at the C/EBP binding sites of the TACE gene. In established rat SH, $1,25(OH)_2D$ synergy with Erlotinib to suppress parathyroid TACE and, consequently, parathyroid cell growth, associated with a 2-fold increase in C/EBPβ levels compared to rats receiving vehicle or either monotherapy ($p < 0.05$; data not shown). Also in A431 cells, a human epidermoid carcinoma cell line that mimics hyperplastic parathyroid cells in TGFα TACE, and VDR expression, $1,25(OH)_2D$ synergy with Erlotinib in inhibiting TACE expression and growth rates, also involves increases in C/EBPβ levels and a 5-fold suppression of TACE promoter activity (not shown).

Importantly, at early stages of kidney disease, the adequate correction of vitamin D deficiency appears to suffice to overcome the resistance to $1,25(OH)_2D$ suppression of increases in parathyroid TACE content and TACE-driven gland enlargement caused by reductions in parathyroid VDR content. In fact, in 5/6 NX rats of 250 g of body weight (10 ml blood volume), early administration (starting 1 week after 5/6NX for 3 weeks) of a combination of 800 ng 25-hydroxyvitamin D weekly plus 16 ng of paricalcitol, a less calcemic $1,25(OH)_2D$ analog, thrice weekly was more effective than 25(OH)D alone to raise serum 25(OH)D levels above 35 ng/ml, a threshold required to suppress PTH at early stages of human CKD [18], and than paricalcitol alone to prevent the increases in parathyroid TACE (not shown) and gland growth (vehicle: 757 ± 64 μg; $n = 6$ vs. Vitamin D: 507 ± 63 μg; $n = 5$). Serum $1,25(OH)_2D$ levels were similar in rats receiving paricalcitol alone or the combination. Therefore, the increases in serum 25(OH)D above 35 ng/ml can partially account for the higher potency of the combination in preventing parathyroid gland enlargement. Elevations in serum 25(OH)D could correct the defective paricalcitol activation of the VDR to suppress TACE either directly, through 25(OH)D binding and activation of parathyroid VDR, or indirectly, through the enhancement of parathyroid $1,25(OH)_2D$ synthesis and autocrine/paracrine VDR activation. Taken together, these findings suggest that parathyroid TACE activation is a key determinant of TGFα-driven hyperplasia in kidney disease. Effective correction of the vitamin D and/or $1,25(OH)_2D$ deficiency of early and advanced kidney disease, by preventing increases in parathyroid TACE, should impede the onset of SH and/or attenuate its progression. Paricalcitol inhibition of proteinuria and, consequently, of the urinary loss of 25(OH)D bound to vitamin D binding protein, could contribute to the higher efficacy of the combination to raise serum 25(OH)D compared to exclusive 25(OH)D dosage.

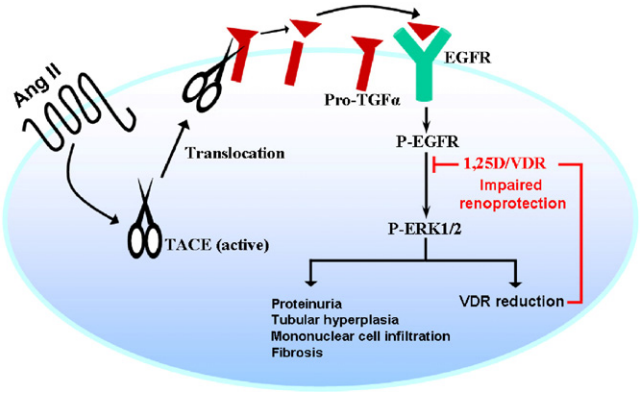

Fig. 5. Increases in renal TACE and not hypertension mediate AngII-driven renal lesions in CKD. Ang II binding to its AT1 receptor induces increases in cytosolic TACE, and its translocation to the plasma membrane. TACE releases TGFα from its transmembrane precursor, which then binds and activates the EGFR causing proteinuria, tubular hyperplasia, fibrosis, mononuclear cell infiltration. TGFα/EGFR-driven VDR reduction impairs $1,25(OH)_2D$ (1,25D)/VDR- renoprotection.

3. Inhibition of renal TACE contributes to $1,25(OH)_2D$ renoprotection

$1,25(OH)_2D$ inhibition of TACE expression and activity in parathyroid and A431 cells has provided a potential mechanism for the renoprotective actions of active vitamin D metabolites unrelated to the suppression of SH, as increases in renal TACE expression have been reported to cause TGFα-driven renal lesions upon nephron reduction, ischemia, or prolonged exposure to angiotensin II (Ang II) in mice [19]. As summarized in Fig. 5, Ang II binding to and activation of Ang II-receptor 1 (AT-R1) enhances TACE expression and activity to release mature TGFα from its transmembrane precursor. Soluble TGFα binds to and activates the EGFR [19] causing

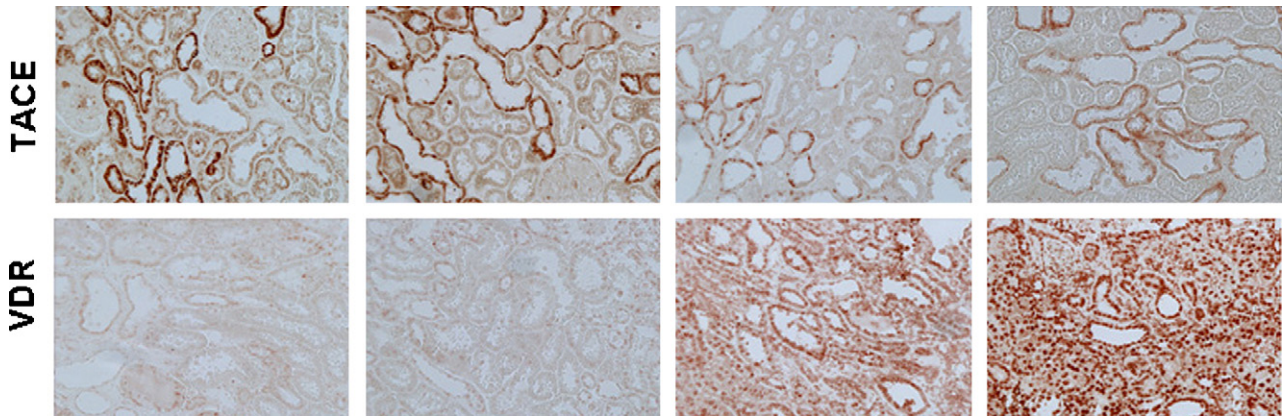

Fig. 6. Increases in renal TACE correlate inversely with VDR content. Representative immunostaining for renal TACE (top panel) and VDR (lower panel) in kidneys from 5/6NX rats.

renal parenchymal lesions, including glomerulosclerosis, tubular atrophy and/or dilation with microcyst formation, mild interstitial fibrosis, and multifocal mononuclear cell infiltration accompanied by severe proteinuria. Consistent with a crucial role of TACE and its activation of the TGFα/EGFR pathway in angiotensin II-driven renal damage, mice that either lack TGFα or express an inactivated-EGFR in renal tubular cells, or wild type mice receiving specific TACE inhibitors are protected from renal lesions during chronic Ang II infusion in spite of hypertension [19]. The same Ang II/TACE-driven mechanism is the cause of renal lesions upon nephron reduction [19], as they can be ameliorated using Ang II-receptor 1 antagonists. Because EGFR activation is known to stabilize TACE protein [11], nephron reduction and elevations in Ang II generate a feed-forward cycle for progressive increases in renal TACE activity and TACE/EGFR-driven renal lesions, thereby impairing not only renal $1,25(OH)_2D$ production by proximal tubules, but also $1,25(OH)_2D$/VDR renoprotection through TGFα/EGFR-driven reductions in renal VDR content. Fig. 6 depicts a strong inverse association between high renal TACE and VDR reduction, as demonstrated in the parathyroid glands [4].

In humans, TACE is constitutively expressed in renal distal tubules and podocytes. Kidney disease induces de novo TACE expression in proximal tubules, peritubular capillaries and glomerular mesangium, and upregulates podocyte TACE content [20]. The increases in glomerular and interstitial TACE expression coincided with enhanced TGFα and associated directly with structural damage, including mesangial matrix expansion, focal glomerulosclerosis, glomerular and interstitial macrophage infiltration, interstitial fibrosis, and decreased renal function, as demonstrated by lower estimated GFR and higher serum creatinine [20]. The adverse effects of renal TACE-driven TGFα activation of the EGFR could also compromise graft survival. In mice, renal EGFR activation was identified as the main determinant of the accelerated progression of renal lesions upon prolonged renal ischemia, a model that mimics the arterial stenosis during transplantation, as kidney damage was markedly reduced in mice carrying a proximal tubule specific EGFR inactivation [21]. Active vitamin D therapy effectively suppresses the TGFα/EGFR pathway in the parathyroid glands [22], and therefore, a similar inhibition of EGFR activation in the kidney could partially account for its renoprotective effects. In fact, in severe proteinuric rats (higher than 2 g of urinary protein per mmol creatinine), EGFR activation was shown to be an important mediator of the endothelial dysfunction that causes the decline in renal blood flow (RBF) during hypertension induced CKD [23]. The inhibition of EGFR activation with small molecule tyrosine kinase inhibitors could restore renal hemodynamics and microvascular hypertrophy, but failed to completely reverse the disease because it has little effect on inflammation [23]. It is unclear from these findings how treatment with TACE inhibitors could prevent macrophage infiltration and fibrosis upon nephron reduction or prolonged exposure to angiotensin II in mice. A likely explanation is that the induction of renal TACE content will not only enhance the release of TGFα to activate the EGFR, but also, of two other TACE substrates from their transmembrane precursors that

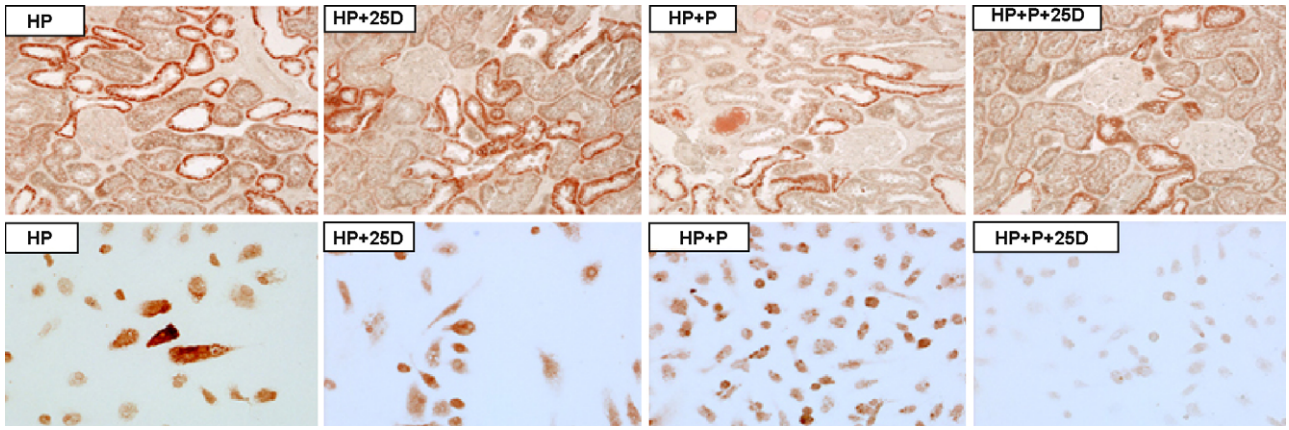

Fig. 7. Early correction of vitamin D deficiency moderates the increases in renal and macrophage TACE. Representative immunostaining for TACE content in kidney sections (top panel) and macrophage derived from bone marrow precursors (bottom panel) from 5/6NX rats fed a high P diet (HP) that were treated for 3 weeks, starting one week after the induction of renal damage, with vehicle, 25-hydroxy vitamin D (25D, once weekly to raise 25D up to 80 ng/ml); paricalcitol (P, 16 ng thrice weekly, a dose insufficient to suppress PTH), or the combination.

are potent pro-inflammatory and pro-fibrotic molecules: the soluble forms of intercellular adhesion molecule 1 (ICAM1) [24] and vascular adhesion molecule 1 (VCAM1) [25,26]. In kidney disease, whereas elevated plasma levels of soluble ICAM1 and VCAM1 correlate indirectly with GFR, soluble VCAM1 correlates directly with fibrinogen expression [27]. Furthermore, elevated serum levels of soluble ICAM1 and VCAM1 molecules are more accurate than proteinuria as markers of endothelial dysfunction and in predicting mortality in renal transplant recipients [28]. The reported increases in renal TACE in human kidney disease also provide some mechanistic understanding for the higher risk of cardiovascular mortality in these patients. TACE also releases the soluble form of the potent inflammatory cytokine TNFα, a critical contributor to systemic inflammation, and a leading cause of renal and cardiovascular damage and arterial calcification [29]. More significantly, a higher risk for cardiovascular mortality occurs in normal individuals carrying a TACE polymorphism that elicits higher TNFα release [30].

Active vitamin D also inhibits the renin–angiotensin system and TGFα/EGFR signaling, and consequently, angiotensin II-driven TACE activation, EGFR-driven renal lesions, and EGFR-driven TACE stabilization suggesting that TACE inhibition could partially contribute to the renal and cardioprotective actions of active vitamin D that are unrelated to PTH suppression. Unpublished observations in the rat model of kidney disease support that an early correction of vitamin D deficiency effectively moderates the elevations in renal and macrophage TACE content (Fig. 7). The reduced renal and macrophage TACE content associated directly with the halting TACE-driven proteinuria and a 70% decrease in aortic calcium deposition (not shown). A similar inhibition of renal TACE by active vitamin D therapy could occur in humans, and consequently, the reductions in serum levels of the markers of TACE activation TGFα, TNFα, ICAM1 and VCAM1 could reflect the efficacy of a safe vitamin D intervention in attenuating TACE-driven renal and cardiovascular lesions.

In summary, our preliminary findings in the rat model of kidney disease constitute the first demonstration of the anti-TACE properties of vitamin D. They suggest that a defective inhibition of parathyroid, renal, and/or macrophage TACE, caused by the vitamin D and/or $1,25(OH)_2D$ deficiency of CKD, could trigger the onset and progression of SH, renal lesions, and systemic inflammation that aggravate renal and cardiovascular damage and predispose to arterial calcifications. The confirmation of the accuracy of serum markers of TACE activity to reflect renal and cardiovascular lesions in experimental kidney disease should help monitor the efficacy of treatment with vitamin D and/or $1,25(OH)_2D$ or its analogs to inhibit renal (and/or macrophage) TACE and to customize therapy in a PTH-independent manner to improve outcomes in transplant recipients and in CKD patients.

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