Interaction of tumor cells with infiltrating lymphocytes via CD70 and CD27 in clear cell renal cell carcinoma

Melanie Ruf*, Holger Moch, and Peter Schraml

Institute of Surgical Pathology; University Hospital Zürich; Zürich, Switzerland

Keywords: CD70, CD27, clear cell renal cell carcinoma, soluble CD27, von Hippel-Lindau gene

CD70 upregulation by hypoxia-inducible factor and CD27⁺ lymphocyte tumor infiltration are associated with worse survival in von Hippel-Lindau gene (VHL) mutated clear cell renal cell carcinoma (ccRCC). CD70/CD27 interaction is accompanied by high soluble CD27 levels in the sera of ccRCC patients suggesting that soluble CD27 is a potential predictive tool for anti-CD70 therapy.

CD70 belongs to the tumor necrosis factor (TNF) ligand superfamily and is typically present on activated B and T lymphocytes, natural killer (NK) cells and mature dendritic cells (DCs). Immunohistochemical (IHC) analysis of several hundred renal cell carcinomas (RCCs) revealed elevated CD70 protein expression in about 80% of primary tumors and metastases of clear cell renal cell carcinoma (ccRCC).¹ A similar high expression frequency of CD70 was not reported for any other solid tumor types² thus making CD70 an auspicious therapeutic target for ccRCC. Studies elucidating the mechanism of CD70 upregulation and the role of CD70 interaction with its unique receptor CD27 in ccRCC are necessary to develop and optimize appropriate diagnostic and therapeutic tools, but these have been lacking so far.

The deregulation of the von Hippel-Lindau protein (pVHL)/hypoxia-inducible factor (HIF) axis is a hallmark of ccRCC. In this particular tumor subtype, we have identified that abundant CD70 leads to anastatic lesions,¹ it is conceivable that the co-existence of CD70 on tumor cells and CD27 co-stimulation in ccRCC. Studies elucidating the mechanism of CD70 upregulation and the role of CD70 interaction with its unique receptor CD27 in ccRCC are necessary to develop and optimize appropriate diagnostic and therapeutic tools, but these have been lacking so far.

In transgenic mice, it has been shown that constitutive expression of CD70 on B cells or dendritic cells stimulates a rapid CD27-mediated phenotypic conversion of naïve T cells to effector cells, which culminates in the depletion of naïve T cells thereby leading to lethal immunodeficiency.⁴ In addition, fewer naïve and central memory T cell subpopulations contrasting with increased numbers of effector memory cells have been detected in ccRCC tumors than among peripheral blood mononuclear cells (PBMCs) from the same patients.⁵ This study also showed that CD70 combined with a T-cell receptor stimulus is sufficient to induce the differentiation of naïve human T cells. This phenotypic conversion was also CD70-dose-dependent.⁵ Consistent with these findings our results suggest that the co-existence of CD70 on tumor cells and CD27⁺ TILs fosters immune “exhaustion effects” by chronic CD70/CD27 co-stimulation in ccRCC.

In our in vitro experiments co-culturing of PBMCs with RCC cells resulted in a CD70-dependent increase in soluble CD27 (sCD27) in the culture supernatant. A similar effect may explain why

¹Correspondence to: Melanie Ruf; Email: melanie.ruf@usz.ch
Submitted: 05/04/2015; Accepted: 05/04/2015
http://dx.doi.org/10.1080/2162402X.2015.1049805

http://oncoline.com
sCD27-concentrations in sera of patients with CD70-expressing ccRCC infiltrated by CD27⁺ lymphocytes have been observed to be significantly higher than those in sera of either patients with tumors negative for CD70 and CD27 or healthy probands. Huang and colleagues showed that the extracellular domain of CD27 is released after lymphocyte activation and engagement of CD70. Release of the ectodomain of CD27 during the course of in vitro activation occurred with minimal cell death, indicating that sCD27 production resulted from shedding by metalloproteinases from the T-cell surface rather than from T-cell apoptosis. Based on these data taken together with our own, we believe that CD70/CD27 interaction likely boosts the release of sCD27 into the sera of ccRCC patients.

As sera levels of CD70 are below the detection limit, the analysis of sCD27 may serve as a potential surrogate marker for CD70 expression. CD70 rather than CD27 is considered a main target for the treatment of ccRCC patients. CDX-1127 is a potent anti-CD27 agonist that induces robust antitumor responses primarily in patients with lymphoid malignancies expressing high levels of CD27. Four anti-CD70 antibody-drug conjugates, MDX-1203, MDX-1411, SGN-75 and SGN-CD70A, have shown promising antitumor activity in CD70-expressing RCC mouse xenograft models and some Phase I clinical trials for metastatic ccRCC are underway.

Provided the application of antibody-drug conjugates show significant response rates in further clinical trials, theragnostic approaches suitable for selecting those ccRCC patients who are likely to benefit from anti-CD70 therapy are required (Fig. 1). These include: i) the pathological determination of the clear cell subtype of RCC and detection of CD70 expression, as well as the presence of CD27⁺ tumor-infiltrating lymphocytes; ii) the treatment of ccRCC patients with an appropriate anti-CD70 drug; and iii) the analysis of sCD70 in patient sera to monitor and survey the clinical course of the disease. Although this scenario is conceivable, a number of retrospective and prospective studies will be required to confirm and validate these data.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Funding
This study was supported by the Swiss National Cancer Foundation to HM (3238BO-10314) and the Zurich Cancer League to HM.

References
1. Ruf M, Mittmann C, Nowicka AM, Hartmann A, Herrmann T, Poyer C, van den Broek M, Sulser T, Moch H, Schraml P, pVHL/HIF-regulated CD70 expression is associated with infiltration of CD27⁺ lymphocytes and increased serum levels of soluble CD27 in clear cell renal cell carcinoma. Clin Cancer Res 2015; 21:889-98; PMID:25691774; http://dx.doi.org/10.1158/1078-0432.CCR-14-1425
2. Grewal IS. CD70 as a therapeutic target in human malignancies. Expert Opin Ther Targets 2008; 12:341-51; PMID:18269343; http://dx.doi.org/10.1517/1478222.12.3.341
3. Noite MA, van Olffen RW, van Gieson GP, van Lier RA. Timing and tuning of CD27/CD70 interactions: the impact of signal strength in setting the balance between adaptive responses and immunopathology. Immunol Rev 2009; 229:216-31; PMID:19426224; http://dx.doi.org/10.1111/j.1600-065X.2009.00774.x
4. Teseler K, Arsen R, van Schijndel GM, Baas PA, van der Valk MA, Bonz J, van Oers MH, van Lier RA. Lethal T cell immune deficiencies induced by chronic costimulation via CD27/CD70 interactions. Nat Immunol 2003; 4:49-54; PMID:12469117; http://dx.doi.org/10.1038/ni869
5. Wang QJ, Hanada K, Robbins PF, Li YF, Yang JC. Distinctive features of the differentiated phenotype and infiltration of tumor-reactive lymphocytes in clear cell renal cell carcinoma. Cancer Res 2012; 72:6119-29; PMID:23071666; http://dx.doi.org/10.1158/0008-5472.CAN-12-0588
6. Huang J, Jochems C, Anderson AM, Talase T, Jales A, Madan RA, Hodge JW, Tsang KY, Liebherr DJ, Steinberg SM, et al. Soluble CD27-pool in humans may contribute to T cell activation and tumor immunity. J Immunol 2013; 190:6250-8; PMID:23677477; http://dx.doi.org/10.4049/jimmunol.1300022
7. Ansell S. A phase I study of an agonist anti-CD27 human antibody (CDX-1127) in patients with advanced hematologic malignancies or solid tumors. J Immunother Cancer 2013; 1(Suppl 1):P259; http://dx.doi.org/10.1186/2051-1426-1-S1-P259
8. Conti A, Santoni M, Amanatini C, Barattini L, Berardi R, Santoni G, Caccini S, Muzonigio G. Progress of molecular targeted therapies for advanced renal cell carcinoma. Biomol Res 2013; 2013:419176; PMID:24093097; http://dx.doi.org/10.1155/2013/419176
9. Seattle Genetics I. Seattle genetics initiates phase I clinical trial of antibody-drug conjugate SGN-CD70A for non-Hodgkin lymphoma and renal cell carcinoma. 2014. Available at http://investor.seattlegenetics.com/phoenix.zhtml?c=124860&p=irol-newsArticle&ID=1957822

Figure 1. Potential theragnostic strategy to diagnose and treat CD70-expressing ccRCC. (1) CD70 upregulation in VHL mutated ccRCC by HIF. (2) Visualization of ccRCC cells and tumor infiltrating lymphocytes (TILs) with hematoxylin and eosin (top); Immunohistochimical staining of CD70 in tumor cells (middle) and of CD27 in lymphocytes (bottom) (10-fold magnification). (3) Soluble CD27 (sCD27) in the sera of ccRCC patients as potential marker for clinical surveillance. (4) Targeting CD70 expressing ccRCC with therapeutic antibody-drug-conjugates which (a) disrupt microtubules, (b) alkylate DNA or (c) induce cellular cytotoxicity.