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Response

Decoy receptor 3 (DcR3), a pleiotropic immunomodulator

Roosneck et al speculated that "any protein carrying an HSPG binding domain fused to the Fc portion of IgG may achieve immunosuppression" based on their observation of the inhibitory effects of TACI-Fc versus BCMA-Fc, and Fc-APRIL versus its mutants Fc-APRIL-H98 and ACRP.Fc. They also speculated that this feature is likely to constitute an advantage to use TACI-Fc in autoimmune disorders. The first speculation is in accord with our observation that HBD.Fc, the recombinant protein comprising the heparan sulfate-binding domain (HBD) of DcR3 and Fc portion of human IgG1, functions as DcR3.Fc does to induce dendritic cell (DC) apoptosis.[1] However, more experiments are needed to consolidate this argument, such as using recombinant proteins comprising the consensus sequences of HBD fused with IgG1.Fc to compare their effects with DcR3.Fc and HBD.Fc to induce DC apoptosis,[1] modulate the differentiation and activation of DC and macrophage,[2,3] activate PKC-delta,[1,4] and enhance osteoclast differentiation.[5] These experiments will provide information to support, or against, their second speculation.

No doubt oligomerized DcR3 is more potent than monomeric DcR3,[3] and DcR3 fused with Fc or another tag might enhance DcR3 activity by increasing stability, dimerization, or oligomerization. However, endogenous DcR3 without Fc still has effects similar to DcR3.Fc because the modulatory effects of DcR3.Fc are also observed in transgenic mice overexpressing DcR3.[6,7] Recently, we further demonstrated that DcR3.Fc is able to down-regulate the expression of the master regulator of MHC-II expression (CIITA) in tumor-associated macrophages (TAM) in vitro, and this is confirmed in the TAMs derived from transgenic mice and cancer patients with up-regulated DcR3.[8] Therefore, like APRIL,[9] endogenous DcR3 might be able to bind to extracellular matrix or to proteoglycan-positive cells to induce oligomerization, and is as potent as, or similar to, DcR3.Fc.

In addition to interacting with proteoglycan, DcR3 also interacts and neutralizes the functions of 3 members of the tumor necrosis factor (TNF) superfamily: Fas ligand (FasL),[10] LIGHT,[11] and TL1A.[12] Previous studies have shown that DcR3 inhibits FasL-mediated apoptosis[7] and enhance angiogenesis via neutralizing TL1A in vivo.[13] Therefore, the newly identified action in DC apoptosis is one of the pleiotropic effects of DcR3 to promote tumor growth.

Several reports have shown that higher serum level of DcR3 correlates with poor prognosis of cancer patients,[8,14-16] and the presence of DcR3 correlates with resistance to 5-fluorouracil–based adjuvant chemotherapy.[17] Therefore, serum level of DcR3 is not only a useful marker to predict cancer prognosis, but is also an important parameter to predict tumor resistance to certain chemotherapy.

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To the editor:

WSU-WM and BCWM.1 should not be assumed to represent Waldenström macroglobulinemia cell lines

Cell line models of malignancy have been invaluable tools in understanding the genetics and cell biology of cancer. Unfortunately, valid cell lines are lacking for Waldenström macroglobulinemia (WM).

It should not be taken for granted that a cell line reported to have been established from a human tumor represents the malignant clone. Most commonly, putative tumor-derived B-cell lines turn out to be bystander B cells immortalized by spontaneous infection with Epstein-Barr virus (EBV), which has not been reported to transform WM cells. Another problem arises from inadvertent cross-contamination of cell lines. This can be difficult for individual investigators to identify, but the application of DNA fingerprinting techniques at large repositories can allow for precise and unique identification for each cell line. At the German Collection of Microorganisms and Cell Cultures, DSMZ, 29% of human tumor cell lines deposited were recently demonstrated to be false, cross-contaminating cell lines.[1] For example, WSU-ALCL was identified to be a T-cell acute lymphoblastic leukemia (ALL) cell line (CCRF-CEM), and WSU-CLL a pre-B cell ALL cell line (REH).[2]

Blood published a report of a putative Waldenström cell line, WSU-WM, in 1993.[3] Although the cell line is EBV-negative, no evidence is presented that it is derived from the index patient. Yet evidence is presented that it is unrelated to the malignant clone: the patient's WM expressed IgM-κ, whereas the cell line expresses IgM-λ. The authors suggest that this could be the result of switching of the light chain, but, given the concerns listed above, this would appear to be the least likely explanation. Although not widely used for many years until a report in this journal in 2003,[4] it has been used extensively since then.[5-14] Until proven otherwise, the WSU-WM cell line should not be viewed as representing a genuine cell line established from the malignant WM clone in this patient.

In 2007 a report appeared in *Experimental Hematology* describing another putative WM cell line, BCWM.1,[15] use of which has also been reported in several recent publications.[9-14,16,17] This study does not report the light chain secreted by the primary tumor. The study's authors performed single-nucleotide polymorphism analysis on the cell line and tumor but do not present the data to indicate that the cell line is derived from the index patient. They performed gene expression profiling on the cell lines and tumor, but this does not confirm a clonal relationship. Regrettably, the one test that could have confirmed or refuted a clonal relationship, IgH CDR3 length analysis, was reported for the cell line but not for the tumor. Finally, the authors reported that the cell line expresses EBV latent membrane protein 1 (LMP1). Until proven otherwise, this cell line should be assumed to be a lymphoblastoid cell line that was derived by EBV transformation of a bystander B cell.

The problems described here are by no means unique to WM or to any particular set of investigators. Despite calls to the contrary, EBV-transformed B-cell lines derived from multiple myeloma (MM) patients continue to be used as models of MM, including ARK, ARH77, MC/CAR, HS-Sultan, and UCLA-1. Furthermore, the extent of cross-contamination of cell lines occurring within labs that carry multiple different lines is often unknown or overlooked.

Given the powerful molecular tools that can be used to verify the identity of established lines, it is important to define a unique set of genetic markers for each line so that individual labs can readily confirm that cell line mix-ups are not a complicating issue for their studies.

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