To the editor:

Heparan sulfate proteoglycans, Fc receptors, and DC suppression

In their recent article in *Blood*, You et al hypothesized on the mechanism by which decoy receptor 3 (DcR3), a member of the tumor necrosis factor receptor family (TNF-R), could promote tumor growth in patients with cancer. They reported that DcR3 induces apoptosis of dendritic cells (DCs) by binding to their heparan sulfate proteoglycans (HSPG). They argued that the ensuing immune suppression would explain why high levels of DcR3 are associated with reduced survival in cancer patients. This effect of DcR3 was shown by using a recombinant form of DcR3 fused to the Fc portion of human IgG1 (DcR3-Fc). However, it is known that the Ig moiety of fusion proteins bind Fc receptors (FcR). Because DCs express high-affinity FcR that can produce a strong signal into cells, the results from You et al do not establish that, without this Ig-FcR interaction, the binding of DcR3 to HSPG is sufficient to induce DC apoptosis. As a consequence, it is not known whether the native form of DcR3 can be held responsible for reduced survival of cancer patients by inducing apoptosis in DCs or, alternatively, by its decoy activity on proapoptotic molecules such as Fas ligand.

Using another member of the TNF-R family, the transmembrane activator, calcium modulator, and cyclophilin ligand interactor (TACI)–Fc, we observed a similar inhibition of DC generation from peripheral blood monocytes (Figure 1A top) as reported by You et al with DcR3-Fc. It is noteworthy that TACI, like DcR3, has an HSPG-binding domain. By contrast, B-cell maturation antigen (BCMA)–Fc that binds the same ligands as TACI-Fc but has no HSPG binding domain failed to inhibit DC generation. This suggests that the HSPG binding domain is essential for the inhibition of DC generation. Such inhibition of DC generation was also observed with a member of the TNF-R family, TACI-Fc in autoimmune disorders.

The finding that simultaneous cross-linking of FcR and HSPG and/or bridging FcR and HSPG eliminates DCs and may cause immune suppression is of great interest. Indeed, any protein carrying an HSPG-binding domain fused to a Fc portion of IgG may achieve immunosuppression. Such immunosuppression is likely to constitute an advantage in the ongoing clinical trial with TACI-Fc in autoimmune disorders.

Eddy Roosnek, Pascal Schneider, and Bertrand Huard

Acknowledgment: This work was supported by the Swiss National Science Foundation, the Foundation Leenaards, and Dr Henri Dubois Firmin-Duru Lipatti Foundation.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Dr Bertrand Huard, Division of Hematology, Geneva University Hospital, 1 Rue Michel Servet, Geneva, Switzerland 1211; e-mail: bertrand.huard@medecine.unige.ch.
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,1,4,5 activate PKC-delta,1,4,5 and enhance osteoclast differentiation.1,4 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 apoptosis7 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,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.

Shie-Liang Hsieh

Conflict-of-interest disclosure: The author declares no competing financial interests.

Correspondence: Shie-Liang Hsieh, Professor, Department of Microbiology and Immunology, National Yang-Ming University, 155, Sec. 2, Li-Nong Street, Shih-Pai, Taipei, Taiwan 11211; e-mail: sshsieh@ym.edu.tw; sshsieh@gate.sinica.edu.tw.

Response

References

Heparan sulfate proteoglycans, Fc receptors, and DC suppression

Eddy Roosnek, Pascal Schneider and Bertrand Huard