Does Erythropoietin Promote Tumor Growth?

To the Editors: In the August 15, 2007 issue of *Clinical Cancer Research*, Saintigny et al. reported the expression of erythropoietin (Epo) and Epo receptor (EpoR) in stage I non–small cell lung cancer (1). They showed that Epo/EpoR coexpression is associated with poor survival in stage I non–small cell lung cancer and suggested a potential paracrine and/or autocrine role of endogenous Epo in non–small cell lung cancer aggressiveness. If these conclusions were supported by convincing evidence, it could have a significant effect on patient care as ~300,000 patients take Epo each year. Saintigny et al.'s conclusions, however, are not convincing due to the lack of rigorous scientific evidence.

First, the EpoR antibody used in this report was not specific enough to use in immunohistochemistry techniques. Elliot et al. found that the C-20 antibody (Santa Cruz Biotechnology) not only detects EpoR, but also cross-reacts with heat shock protein 70 (HSP70) at a different molecular weight (2). In addition, HSP70 is found at high levels in tumors (2). Independently, Della Ragione et al. have confirmed the HSP70 detection by C-20 antibody in two human leukemic lines (3). In addition, H-162 antibody (Santa Cruz Biotechnology) against Epo has low specificity. The Saintigny et al. study would be acceptable if it were validated by monospecific antibodies against Epo and EpoR, and shows that positive results are still present by HSP70 peptide pretreatment as well as being abrogated by pretreatment with Epo and EpoR peptides.

Furthermore, Saintigny et al. described that Epo and EpoR were detected mainly in the cytoplasm, in only a few cases were they cell surface–bound (1). This data raises the question: are the endogenous Epo and EpoR in the cytoplasm functional? To address this, the demonstration of endogenous Epo/EpoR activity is mandatory (i.e., providing evidence of Epo signaling, and analyzing cell proliferation and apoptosis assays). Saintigny et al. referred to works from other researchers to show functional Epo/EpoR signaling in many cancer cells. These reports, however, show the effects of extracellular Epo. To our knowledge, there are no published data proving the functionality of intracellular Epo and EpoR.

The nonerythroid effects of Epo are real and likely both beneficial (decreased ischemic area of the brain), as well as detrimental (4); others likely exist but these need to be proved by more convincing evidence than that presented by Saintigny et al. (1), as we previously proposed in our comment on the study by Henke et al. (5).

Donghoon Yoon
Neeraj Agarwal
Josef T. Prchal
Hematology/Oncology, University of Utah, Salt Lake City, Utah

References

1. Saintigny P, Besse B, Callard P, et al. Erythropoietin and erythropoietin receptor coexpression is associated with poor survival in stage I non-small cell lung cancer. Clin Cancer Res 2007;13:4825–31.
2. Elliott S, Busse L, Bass MB, et al. Anti-Epo receptor antibodies do not predict Epo receptor expression. Blood 2006;107:1892–5.
3. Della Ragione F, Cucciolla V, Borriello A, Oliva A, Perrotta S. Erythropoietin receptors on cancer cells: a still open question. J Clin Oncol 2007;25:1812–3; author reply 5.
4. Prchal JT, Semenza GL, Prchal J, Sokol L. Familial polycythemia. Science 1995; 268:1831–2.
5. Agarwal N, Gordeuk VR, Prchal JT. Are erythropoietin receptors expressed in tumors? Facts and fiction—more careful studies are needed. J Clin Oncol 2007; 25:1813–4.

doi:10.1158/1078-0432.CCR-07-4612

Clinical Cancer Research

Does Erythropoietin Promote Tumor Growth?

Donghoon Yoon, Neeraj Agarwal and Josef T. Prchal

Clin Cancer Res 2008;14:1920.