

Breakthrough in tracking tumor erythropoietin receptor expression

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Erythropoietin (EPO) was discovered more than one century ago as hemopoietin, a plasmatic humoral factor essential for red blood cell development (1). It was later described as a 34-kDa glycoprotein of 165 amino acids acting as a hormone, cytokine and growth factor (2). In adults, kidneys and liver are considered main and secondary EPO production sites, respectively. EPO is a key cytokine for erythroid development through its interaction with its erythroblast membrane receptor (EPOR). Until recently, EPOR's role was attributed exclusively to erythroid proliferation, differentiation and survival.

However, many recent studies described non-hematopoietic expression of EPOR in brain, heart, small bowel, uterus, kidney and pancreatic islets. Interestingly, these results suggested EPO as a regulator of development and differentiation also in non-hematopoietic tissues. By now it is well accepted that EPO exerts cytoprotective effects against apoptosis and inflammation in non-erythroid tissues further extending the range of clinical applications of recombinant human erythropoietin (rhuEPO). Numerous promising rhuEPO molecules mimicking all properties of native EPO have been engineered to improve specificity and efficiency as cytoprotective agents with reduced side effects. Cardioprotection and neuroprotection are the main areas investigated for protective applications of erythropoietin (1).

In order to compensate loss of EPO production after renal failure, cancer or cancer therapy, rhuEPO is currently prescribed to alleviate anemia. However, chronic inflammation is one of the main causes of anemia in cancer patients and rhuEPO-mediated erythropoiesis of progenitor stem cells was reported as strongly affected by pro-inflammatory cytokine TNF α (3). Furthermore, use of rhuEPO for the treatment of anemia of cancer was strongly

suspected to activate tumor cell proliferation in clinical studies (4). Accordingly, this therapy requires care and specific recommendations were emitted from US Food and Drug Administration (FDA) (5). Nonetheless, discovery that many cancer cell types express EPOR has to be considered with care as specific antibodies allowing detection and/or quantification of this receptor were lacking until now. Even though some anti-EPOR antibodies were commercially available, their specificity was a matter of controversy (6,7) and their use described inappropriate in specific applications including cytometry analysis.

Dennis Doleschel and coll., describe here a suitable and elegant technical solution to identify and to quantify EPOR expression on cellular surfaces. By coupling a near-infrared dye (Cy5.5) to rhuEPO (epoetin β) they designed a molecular tool allowing high affinity detection of EPOR expression. They included convincing controls that clearly validated the efficiency of this novel "molecular probe". One of the advantages of their hybrid molecule is the reduced impact on physical properties of rhuEPO, which consequently preserved biological activity after comparison with non-transformed rhuEPO on several tumor cell lines *in vitro*. Importantly, the conjugated molecule was well tolerated in animals and its usefulness was demonstrated by *in vivo* imaging of EpoR in tumor tissues by fluorescence-mediated tomography (FMT).

Use of this generation of molecular tools should be of high relevance in *in vitro* as well as *in vivo* studies in order to improve characterization of EPOR expression in tumor cells as it was clearly demonstrated in this article. Here, the authors focused on the technical validation using non-small cell lung cancer cell lines as a model.

What is the effect of rhuEPO on cell proliferation related

to the level of EPOR expression in tumor cells? Obviously, they could not yet provide a conclusive answer to this essential question, which would be of importance to manage anemia treatment of cancer patients. An in-depth understanding of the effects of rhuEPO on cancer cell proliferation and survival will also eventually be improved by the use of rhuEPO-Cy5.5 conjugates and future analogs. The design of this probe clearly represents a breakthrough in medical imaging that will be likely to be further enhanced by the development of conjugates for positron emission tomography (PET) technology exhibiting better tissue penetration depth compared to FMT. *In vivo* tracking of erythropoietin receptor in human tumors will then become a reality!

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