Targeting tumour hypoxia to prevent cancer metastasis. From biology, biosensing and technology to drug development: the METOXIA consortium.

Abstract:
The hypoxic areas of solid cancers represent a negative prognostic factor irrespective of which treatment modality is chosen for the patient. Still, after almost 80 years of focus on the problems created by hypoxia in solid tumours, we still largely lack methods to deal efficiently with these treatment-resistant cells. The consequences of this lack may be serious for many patients: Not only is there a negative correlation between the hypoxic fraction in tumours and the outcome of radiotherapy as well as many types of chemotherapy, a correlation has been shown between the hypoxic fraction in tumours and
cancer metastasis. Thus, on a fundamental basis the great variety of problems related to hypoxia in cancer treatment has to do with the broad range of functions oxygen (and lack of oxygen) have in cells and tissues. Therefore, activation-deactivation of oxygen-regulated cascades related to metabolism or external signalling are important areas for the identification of mechanisms as potential targets for hypoxia-specific treatment. Also the chemistry related to reactive oxygen radicals (ROS) and the biological handling of ROS are part of the problem complex. The problem is further complicated by the great variety in oxygen concentrations found in tissues. For tumour hypoxia to be used as a marker for individualisation of treatment there is a need for non-invasive methods to measure oxygen routinely in patient tumours. A large-scale collaborative EU-financed project 2009-2014 denoted METOXIA has studied all the mentioned aspects of hypoxia with the aim of selecting potential targets for new hypoxia-specific therapy and develop the first stage of tests for this therapy. A new non-invasive PET-imaging method based on the 2-nitroimidazole [(18)F]-HX4 was found to be promising in a clinical trial on NSCLC patients. New preclinical models for testing of the metastatic potential of cells were developed, both in vitro (2D as well as 3D models) and in mice (orthotopic grafting). Low density quantitative real-time polymerasechain reaction (qPCR)-based assays were developed measuring multiple hypoxia-responsive markers in parallel to identify tumour hypoxia-related patterns of gene expression. As possible targets for new therapy two main regulatory cascades were prioritised: The hypoxia-inducible-factor (HIF)-regulated cascades operating at moderate to weak hypoxia (<1% O(2)), and the unfolded protein response (UPR) activated by endoplasmatic reticulum (ER) stress and operating at more severe hypoxia (<0.2%). The prioritised targets were the HIF-regulated proteins carbonic anhydrase IX (CAIX), the lactate transporter MCT4 and the PERK/eIF2α/ATF4-arm of the UPR. The METOXIA project has developed patented compounds targeting CAIX with a preclinical documented effect. Since hypoxia-specific treatments alone are not curative they will have to be combined with traditional anti-cancer therapy to eradicate the aerobic cancer cell population as well.