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Oxygen tension governs the crosstalk between the tumor and its microenvironment: angiogenesis should be the target of therapies

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Abstract of the lecture

Hypoxia makes cancer an angiogenesis-dependent disease. Impaired O2-delivery contributes to tumor growth, metastasis and selection of aggressive cancer stem-like cells. Metabolism of tumor cells and cells that participate to their microenvironment is ruled by the hypoxic state, the key parameter of related studies. Thus, hypoxia alleviation is the challenge of therapeutic strategies aiming to render the tumor sensitive to the immune response.

Pathologic tumor angiogenesis mean endothelial cells (ECs) damage, a key event occurring at the angiogenic switch. It is favored by the particular aerobic glycolytic metabolism of ECs, making them targets to revert hypoxia through vessel normalization.

Consequently, anticancer strategies directed to pathological angiogenesis aim to normalize the vasculature. This is the challenge of pO2 control strategies to change the tumor microenvironment and the immune tolerance into efficient immune response. In hypoxic angiogenesis, glycosylation-regulation has a strong impact on cell interactions/recognitions, the metastatic process, tumor resistance by cancer-stem-cells and immunosuppression/escape. Immunosuppression occurs via immune checkpoints modulation on ECs, illustrated by the modulation of PD-L1 expression at the EC surface, its increase in hypoxic conditions and preventing recruitment of competent cells to destroy the tumor cells, such as activated T and NK cells. The modulation of the PD-L1/PD1 recognition and expression is a PTEN-dependent process. Tumor suppressor, PTEN is the main control of the PI3K/PDK/AKT/mTOR pathway. Its specifically active glycoforms influence its action. PTEN regulates other tumor suppressors as the von-Hippel-Lindau protein upon PI3K/AKT/mTOR cell growth activating pathway control. This opens a regulatory mean for hypoxia-induced HIF1α and has deep consequences on MDM2 inhibition of the p53 suppressor activity.

Consequently, vasculature normalization obtained by direct O2 delivery increase by red blood cells using an allosteric effector of hemoglobin is of major importance as it also allows stable angiogenesis normalization via PTEN activation activity in endothelial cells.

Short CV of Prof. Claudine Kieda

Research director at CNRS France and coordinator of the French Polish cooperation through the BBiB UJ and CNRS, Centre for Molecular Biophysics/University of Orleans and having presently developed a research laboratory devoted to Molecular Oncology and Innovative Therapies in Warsaw- Poland, Claudine Kieda and the team are focusing on the molecular and cellular mechanisms of targeting and treatment of hypoxia-dependent pathologies.

Elucidation of the mechanisms of the cell cross-talks in hypoxic tumor microenvironment based on the organospecificity and biological response of endothelial cells, allowed the development of our main strategies. Our approaches are devoted to alleviation of hypoxia which mediates the pathologic angiogenesis for its influence on the overall antitumor immune response.

The most important publications:

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