UNIVERSITY OF WARSAW | CeNT CENTRE OF NEW TECHNOLOGIES

invites to a seminar by

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Targeting tumor-microenvironment interactions as a new therapeutic approach

15th of February 2018 at 12 p.m.

Venue: Centre of New Technologies, Banacha 2C,
Lecture Hall 0142 (Ground floor)

Host: Marta B. Wiśniewska

Microglia are innate immune cells residing in the central nervous system that rapidly respond to signals originating in the injured, infected or dysfunctional brain. Microglia are plastic, respond differently to challenges and convert extracellular signals into sustained patterns of gene expression. Global gene expression profiling, functional assays and a comprehensive analysis of biochemical pathways in primary microglia cultures revealed that inflammatory signals and glioma-secreted factors induce signal-specific transcriptional, signaling and metabolic pathways. Malignant glioma cells produce factors that attract and polarize microglia and peripheral macrophages into pro-invasive, immunosuppressive cells. Glioma associated microglia and macrophages (GAMs) stimulate tumor invasion, support tumor progression and contribute to therapy resistance. Tumor-activated GAMs create an immunosuppressive milieu, inhibit responses of infiltrating T cells and support accumulation of T regulatory cells. We identified tumor-derived granulocyte macrophage colony factor (CSF2) and tumor-processed osteopontin/SPP1 as major microglia-activating factors. Osteopontin is a small glycoprotein, interacting via a RGD motif with integrin receptors on immune cells. Tumor-processed Spp1 induces the pro-tumorigenic polarization of microglia *in vitro*. Knockdown of Spp1 in experimental rat C6 gliomas inhibited growth of intracranial gliomas and reduced the number of pro-invasive microglia/macrophages expressing Arg1 and CD163. Moreover, T lymphocytes infiltrating Spp1-depleted gliomas showed signs of restoration of antitumor activity. Using a series of Spp1 mutants we defined protein fragment crucial for interactions with microenvironment. We designed a short RGD peptide interfering with osteopontin binding and the peptide blocked efficiently migration, phagocytosis and tumor-evoked integrin signaling in cultured microglia. While osteopontin was critical for microglia polarization, CSF2 interacting with its receptor on microglia was essential for microglia infiltration and survival. Tumor-derived CSF2 upregulated its receptor both in human glioma cells and in microglial cells. We developed a series of humanized short peptides interfering with binding of CSF2 or osteopontin to their receptors and selected those with potent activity in blocking microglia-dependent glioma invasion *in vitro*. Moreover, we provide an evidence for anti-tumor activity of water soluble, CSF2 targeting peptides delivered intra-cranially to human U87 gliomas growing in nude mice. In vivo imaging and histological evaluation showed reduction of tumor growth. Our results show that targeting glioma-microglia interactions with short interfering peptides against CSF2 and/or osteopontin could be a novel therapeutic strategy.

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