Laboratory of Tumour Immunology

Anti-tumour immunotherapy, immunoediting, immunoepigenetics, cellular senescence

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As a long-term research programme we have been investigating the interactions between tumour cells and the immune system, with special attention paid to the mechanisms by which the tumour cells are capable to escape from immune responses. Our projects are also focused on the mechanisms of immunosuppression and its possible overcoming and, finally, on experimental anti-tumour immunotherapy and immunologic impacts of chemotherapy. Most of our studies employ murine models for tumours associated with human papilloma virus infection or for prostate cancer. MHC class I deficiency on tumour cells is a frequent mechanism by which tumour cells can escape from specific immune responses. We have found that epigenetic agents, namely DNA methyltransferase inhibitor 5-azacytidine, can induce expression of genes involved in the antigen-processing machinery and surface expression of MHC class I molecules on MHC class I-deficient tumour cells, which was associated with demethylation of the regulatory sequences of the corresponding genes. Activation of the genes encoding the components of the antigen-processing machinery is often mediated by interferon γ. We have demonstrated that gene expression mediated by this cytokine can be associated with DNA demethylation, suggesting that interferon γ can be considered as an epigenetic agent. Our next areas of interest are populations of immunoregulatory cells and their dynamics in the course of the tumour growth and therapy. We are namely interested in myeloid-derived suppressor cells, a cell population playing a critical role in mediating suppression of the anti-tumour immunity. We have found that 5-azacytidine can display both cytotoxic and differentiation effects on these cells. Our interest has also been turned to the field of cellular senescence induction in tumour cells upon treatment with genotoxic agents and to the role of cytokines in the senescence induction and maintenance. We believe that better understanding of the mechanisms by which senescent tumour cells can influence the tumour microenvironment and, on the other hand, whether and how the immune response can induce cellular stress and senescence in tumour cells, can bring clues important for our better insight into the tumour development, as well as for finding new therapeutic schemes. Besides our basic research programme we also perform contract research, mainly dealing with optimization of the dendritic cell-based immunotherapy combined with chemotherapy. Indeed, we are open for collaborations in the field of anti-tumour immuno- and chemotherapy, using our animal models and our immune response-monitoring expertise.

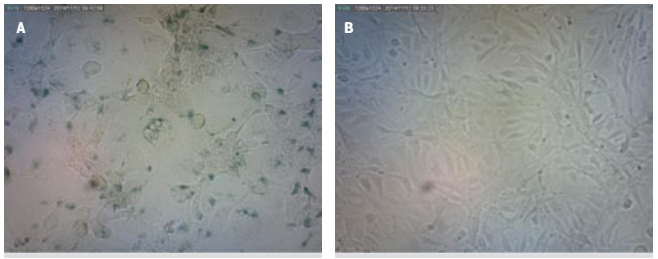
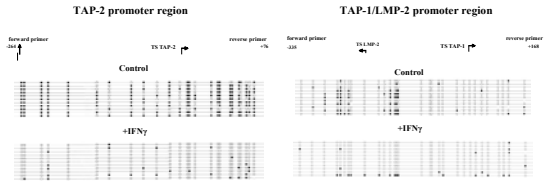


Fig. 2. Induction of cellular senescence in TC-1 tumour cells in response to docetaxel treatment (detected by β-galactosidase staining). Massive cellular senescence (blue stain) can be observed in docetaxel-treated cells (A) but not in control untreated cells (B).

Fig. 1. IFNγ-induced DNA demethylation of the TAP2 and TAP1/LMP2 promoters in TC-1/A9 cells analysed by bisulphite sequencing. DNA isolated from the IFNγ-treated and control untreated MHC class I-deficient TC-1/A9 cells was subjected to bisulphite conversion and cloned. Sequences from 11 clones from each sample are presented. After treatment with IFNγ, strong DNA demethylation of both the TAP2 and TAP1/LMP2 gene promoter regions was observed. White and black circles indicate unmethylated and methylated CpGs, respectively. Gene transcription start sites (TS) are indicated. This DNA demethylation was accompanied by increased MHC class I molecule expression on the cell surface. For details, see Vlkova et al., Oncotarget 2014.



- MH, NT14461 – Senescence cell elimination in minimal residual tumour disease therapy, 2013-2015, M. Reiniš
- GACR, 14-10100S – Utilization of novel mouse strains for investigation of the NK cell regulatory role in development and therapy of cancer, 2014-2016, M. Indrová
- GACR, GAP301/10/2174 – Epigenetic mechanisms in regulation of genes important for antigen presentation and antitumour immunity, 2010-2013, M. Reiniš
- GACR, GPP301/11/P220 – Mechanisms underlying cyclophosphamide-induced accumulation of myeloid derived suppressor cells, 2011-2013, R. Mikyšková

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From the left: Romana Mikyšková, MD, PhD / Research fellow, Jana Bieblová, MSc / Technician, Veronika Polláková, MSc, PhD / Postdoc, Milan Reiniš, PhD / Head of Laboratory, Marie Indrová, PhD / Research fellow, Georg Michlits (from 2014) / PhD student, Oleksander Korolov (from 2014) / PhD student, Renáta Turečková /Technician, Jana Šímová, PhD / Research fellow

Not in the picture: Ivan Štěpánek, Dipl. Ing., MSc, PhD / Postdoc, Lenka Fišerová (from 2014) / Undergraduate student, Michaela Horňáková / Undergraduate student, Magdalena Cebová (until 2013) / Undergraduate student, Veronika Hrušková (until 2014) / Undergraduate student, Zuzana Paračková (until 2013) / Undergraduate student, Lenka Fišerová (from 2014) / Undergraduate student