Laboratory of Tumour Immunology
Anti-tumour immunotherapy, immunoediting, immunoeugenetics, NKT cells, immune suppression
Milan Reiniš
milan.reinis@img.cas.cz

As a long-term research programme of our laboratory we have been investigating the mechanisms by which tumour cells are capable to escape from immune responses. Our projects are focused on regulation of genes encoding molecules crucial for antigen presentation and for tumour cell elimination by specific immune responses, on mechanisms of immunosuppression and its possible overcoming, and, finally, on experimental anti-tumour immunotherapy. Most of our studies employ murine models for tumours associated with human papilloma virus [aetiological agent of the cervical carcinoma]. Special attention has been paid to the setting of the minimal residual tumour disease treatment after primary tumour resection or chemotherapy.

MHC class I deficiency on tumour cells is a frequent mechanisms by which tumour cells can escape from specific immune responses. We have been interested in mechanisms underlying reversible MHC class I downregulation on tumour cells. We have found that epigenetic agents induce expression of genes involved in antigen-processing machinery and surface expression of MHC class I molecules on tumour cells, as well as of selected co-stimulatory and co-inhibitory molecules. Further analysis revealed that MHC class I downregulation in our model cell lines was associated with epigenetic silencing of antigen-presentation machinery genes. Our current projects in this field are focused on in vivo experiments with the aim to optimize immunotherapy of MHC class I-deficient tumours combined with administration of DNA methyltransferase inhibitors. We are also interested in epigenetic mechanisms underlying regulation of genes encoding antigen-presentation machinery genes, as well as co-stimulatory/inhibitory genes in antigen-presenting or regulatory immunocytes.

Our next areas of interest are populations of immunoregulatory cells (NKT, T-regulatory and myeloid-derived suppressor cells) and their dynamics in the course of tumour growth and therapy, as well as their mutual interactions. Recently, we have shown that administration of a glycolipid ligand activating NKT cells, β-D-galactosylceramide, inhibited growth of recurrent MHC class I-positive and -deficient tumours after surgery. Along with these projects we have been interested in experimental anti-tumour immunotherapy and vaccines.

We have been investigating the impacts of several chemotherapeutic agents on anti-tumour immunity and on regulatory cell populations. We have used cell and gene therapy approaches and dendritic cell-based vaccines, as well as genetically modified tumour cells producing cytokines [especially IL-12-producing cells] for vaccination and immunotherapy optimization.

References:
2. GA DR, GA301/09/12094 – Molecular and cellular mechanisms of tumour chemotheraphy: immunomodulatory effect, 2009-2011, M. Indrová
3. GA DR, GAP001/10/2174 – Epigenetic mechanisms in regulation of genes important for antigen presentation and antitumour immunity, 2010-2013, M. Reiniš

Fig. 1. ELISPOT (Enzyme-linked immunosorbent spot) analysis of the spleen cell activation with a ligand for NKT T-cell receptor (C12 β-D-GalactosylCeramide) and its inhibition with the anti-CD1d- antibody demonstrates that the C12 β-D-GalactosylCeramide effects are mediated through its presentation by the CD1d molecules. Each colour spot represents one interferon-γ-producing spleen cell.

Fig. 2. Tumour growth curves in control mice and mice subjected to chemio- and immunotherapy and their combination. Tumour inhibitory effects of combined epigenetic agents, 5-azacytidine (5AC) and immune activator unmethylated oligodeoxynucleotide (CpG 1826), MHC class I-deficient tumour cells were transplanted on day 0. In experimental groups, 5AC was repeatedly administrated on days 3, 7, 10, 14, 17, 21, 28; immune activator, CpG 1826 was administrated on days 3 and 10. Significant inhibition was observed in all treated mice, as compared to the untreated controls. Combined therapy was significantly more effective as compared to monotherapies only.