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Laboratory of Genome Integrity

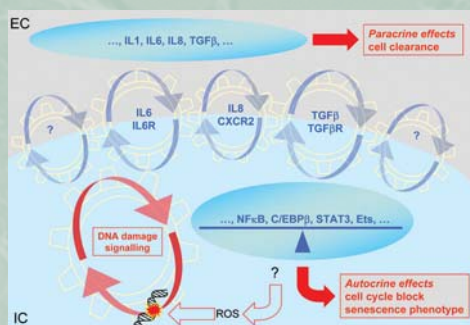
DNA damage response, cell cycle, oncogenic transformation, ageing



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Research topics

The research focus of the group established in January 2008 is centered on the mechanisms of maintenance of genomic integrity, which is a fundamental biological mechanism that care-takes against genetic diseases including cancer. Cellular senescence is one of the barriers guarding the organism against uncontrolled proliferation of cells with damaged genome. We focus on the mechanisms of oncogene- and chemically-induced senescence. We found that human cancer cells forced to chemically-induced senescence produce a large spectrum of cytokines including interferons, IL-1 β , IL-6, IL-8, IL-10 and members of TNF and TGF families as a part of their secretory phenotype. Two of these cytokines, IL-6 and IL-8, play a pivotal role in promotion and maintenance of oncogene-induced senescent phenotype via autocrine regulatory loops. To understand the molecular mechanisms of persistent operation of these loops in senescent cells, we are investigating the role of DNA damage signalling in the regulatory pathways involved in cytokine gene expression, the role of post-translational modifications such as sumoylation in establishment and stabilization of cytokine loops, the role of cytokines in maintenance of the cell cycle arrest characteristic for senescent cells and the paracrine effects of secreted cytokines on surrounding cells - for example, in adaptation of neighbouring cells to DNA damage.



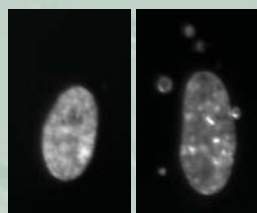
Model of cellular senescence promoted and maintained by concerted action of cytokine autocrine loops and the DNA damage response (DDR). DDR activates specific transcription factors (for example, NF- κ B, C/EBP β), which induce expression of several cytokine genes (for example, IL-1, IL-6, IL-8). Secreted cytokines trigger their respective signalling pathways by autocrine stimulation of plasma membrane receptors. Thus, the combined and interlocked activity of DNA damage and cytokine signalling pathways results in balanced cocktail of activated transcription factors, which induce a specific set of genes responsible for cell cycle block, promotion and maintenance of senescent phenotype, the induction of cytokine transactivator genes themselves and production of reactive oxygen species, which enclose the vicious cycle. EC, IC, extra/intracellular space.

Current grant support

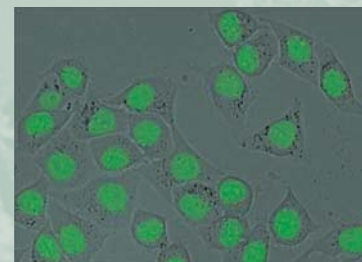
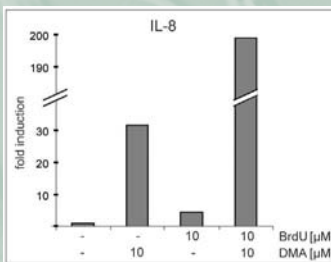
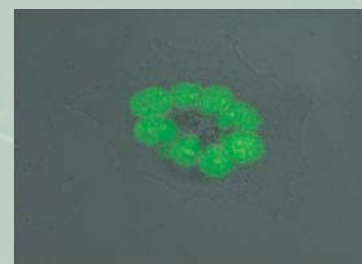
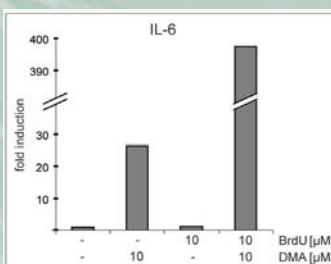
GA AS CR (IAA50039050); GA CR (GA204/081418, GA301/08/0353); FP7-HEALTH-2007-B (223575)

Selected recent papers

1. Bartek J, Hodny Z, Lukas J. Cytokine loops driving senescence. *Nat Cell Biol.* 2008;10:887-889.
2. Novakova Z, Hubackova S, Janderova-Rossmislova L, Dobrovolna J, Vasicova P, Horejsi Z, Hozak P, Bartek J, Hodny Z. Cytokine expression and signaling in chemically induced cellular senescence. (submitted)



Bacterial toxin-induced cellular senescence accompanied by chromosomal aberrations detected as micronuclei. Nucleus of control (left) and intoxicated cell (right).



Interleukins IL-6 and IL-8 elevated in cultivating media of chemically senescent tumour cells

Polynucleation in aphidicolin-induced HeLa senescent cells. Histone-GFP labelled nuclei of normal (top) and senescent cell (bottom)