132

Intracellular bacteria as vaccine carriers – new weapons against cancer?

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Several years ago, intracellular bacteria like mycobacteria, salmonella, listeria and shigella were exclusively considered as dangerous pathogens. The tremendous success in understanding the molecular biology and immunology of these bacteria has opened a very promising way of using attenuated intracellular bacteria as vaccine carriers. Especially for the prevention and therapy of cancer, they possess some attractive features like the preferential induction of a Th1 response, the direct targeting of professional antigen presenting cells and the ease of production.
Here, we want to introduce the technique of DNA delivery with intracellular bacteria and some preliminary results obtained with highly attenuated suicide *Listeria monocytogenes* strains to deliver DNA encoding for oncoproteins.

133

THE PROLIFERATION- ASSOCIATED SUPEROXIDE ANION AND THE DIFFERENTIATION- ASSOCIATED PEROXIDE ANION MAY HELP TO EXPLAIN THE AMBIVALENT ROLE OF P53 AS TUMOR SUPPRESSOR GENE AND AS DOMINANT TRANSFORMING ONCOGENE

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According to our investigations, (a) a high level of HO_2 induces cell proliferation, (b) an increased level of H_2O_2 supports cell differentiation and cell-cycle arrest, and (c) a constitutively increased intramitochondrial/intranuclear HO_2/H_2O_2 ratio seems to represent the "lowest common denominator" of malignant cells. We therefore postulate that all genetic defects (point mutations, deletions, chromosomal translocations etc.), which are associated with a constitutively increased HO_2-production and/or a reduced H_2O_2-generation may result in cell transformation. Moreover, since HO_2 is "neutralized" in a diffusion-limited reaction (K...$6{,}7.10^9\ M^{-1}s^{-1}$) by the NO radical, mutations, resulting in (a partial) cNOS-inactivation may also be considered as contributing to cell transformation. Our observations win a high actuality in connection with the recent report (by H.Tanaka et al.) that one of the p53 target genes (p53R2) corresponds to the R2-subunit of the cytosolic ribonucleotide reductase (RR), coding for NADPH oxidase, SOD and catalase. This triple ROS-modulating enzyme maintains the critical RR tyrosyl radical in its active, dNTP-synthesizing state. Since the dNTP-level decides about proliferation vs.differentiation, the fine tuning of ROS members by both R2 subunits is critical for the control of cell growth. Point mutations which inactivate either (a) the SOD-targeting subunit of p53R2 or (b) both SOD-encoding genes, i.e. the intranuclear and the cytosolic one, lead to the accumulation of the SOD-substrate HO_2 and herewith to an increased HO_2/H_2O_2-ratio. The p53R2 domain is the only one found to be mutated in tumors (G.Lozano & S.J. Elledge). This explains for the first time the controversially discussed p53-function as a suppressor gene and as a dominant transforming oncogene (of the c-myc type) which is able to immortalize different cell types