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Abstracts of Theses from the Nordic Countries

Short abstracts of theses on oncologic subjects are published under this heading. The abstract should contain background, problems, results and conclusions and be an independent informative unit that can be read without access to the thesis. It should not contain references to literature, figures or tables in the thesis. A suitable size is about 500 words. The abstract can be sent to Acta Oncologica together with information about department, faculty and university and date of dissertation.

On the pro-apoptotic mechanisms of the antitumor drugs doxorubicin and interferon-α

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Anti-cancer drugs act primarily by inducing apoptosis. However, knowledge of how various substances induce apoptosis is still incomplete, and so is the basis for the great variation in cellular sensitivity to cytotoxic drugs. A detailed understanding of how anti-cancer agents induce cell death and how defects in cell death pathways promote resistance will change the way chemotherapeutic drugs are used and designed.

The aim of this thesis was to investigate pro-apoptotic signaling induced by two commonly used anti-cancer drugs, Doxorubicin and Interferon-α.

Doxorubicin (DXR), an anthracycline, is a major antitumor agent known to cause cellular damage via a number of mechanisms including free radical formation and inhibition of topoisomerase II. Interferon-α (IFN-α) is a pleiotropic cytokine and its ability to induce apoptosis has been proposed to be of major importance for its clinical anti-tumor activity.

The results demonstrate that the mechanisms of induction of apoptosis by both drugs are strikingly similar with respect to the signaling involved. Clinically relevant concentrations of both agents induce the activation of the pro-apoptotic Bcl-2 family members Bak and Bax prior to apoptosis and anti-apoptotic Bcl-2 family members regulate this response. We could also demonstrate that Bak is activated prior to Bax by both agents. Upstream of Bak, Bax and the mitochondria, two kinases that are known to be activated by cellular stress, JNK and PKCδ, are involved, both with respect to DXR and IFN-α.

We demonstrated the requirement of Bak and Bax for the induction of apoptosis by DXR by using *bax*- as well as *bak*-deficient mouse embryo fibroblasts (MEFs). The BH3-only protein, Bik, which is induced in response to DXR, could be an activator of Bak and Bax. Upstream of the Bcl-2 family members, caspase-2 is activated and was found to be required for DXR-induced apoptosis in Jurkat cells. PKCδ was found to be one of the critical downstream targets of caspase-2 following DXR treatment. By using chemical inhibitors against caspase-2, PKCδ and JNK, our data suggest a signaling model involving caspase-2, PKCδ and JNK.

Survival signaling could mask the true potential of chemotherapeutic agents as demonstrated by co-incubation of a P13K-inhibitor with DXR. Inhibition of P13K potentiated the DXR-induced Bak, Bax activation and apoptosis in a Bcl-2 dependent but in a caspase-2, JNK and PKCδ-independent manner.

The upstream signaling in IFN-α-induced apoptosis was also addressed. Upstream of the mitochondria, IFN-α induces JNK phosphorylation/activation. Inhibition of JNK significantly blocked IFN-α-induced Bak and Bax activation and apoptosis, but did not affect the IFN-α-stimulated Jak/STAT signaling. This suggests that the canonical IFN-α induced pathway is not sufficient for this response. Inhibition of JNK was also found to influence the phosphorylation of the pro-apoptotic PKC family member, PKCδ. Furthermore, PKCδ inhibition blocked apoptosis and Bak activation induced by IFN-α. We conclude that IFN-α-induced apoptosis involves the mitochondrial pathway and the kinases JNK and PKCδ Furthermore this stress-related IFN-induced pathway is unrelated to the Jak/STAT signaling which is generally thought to mediate IFN-α's cellular responses.

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Aspects of gastroesophageal reflux and risk for esophageal cancer—An epidemiological approach

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The aims of this study were to confirm, in a prospective study, the link between gastroesophageal reflux and risk of adenocarcinoma of the esophagus and gastroesophageal junction observed in retrospective studies, to investigate into the effects of anti-reflux surgery, and to shed light on some possible mechanisms behind the alleged carcinogenicity.

We estimated relative risk for esophageal adenocarcinoma in a cohort of 35,274 male patients hospitalized for gastroesophageal reflux disease (GERD) and another cohort of 6,406 male patients who underwent antireflux surgery identified in the Swedish Inpatient Register, using the general Swedish population as reference. Further, in a nationwide population-based case-control study in Sweden, antibodies against *H. pylori* and cytotoxin-associated gene-A-positive (CagA+) antigens, and pepsinogen I concentration were measured using sera from 97 esophageal adenocarcinorfla, 85 esophageal squamous-cell carcinoma patients and 499 randomly selected controls. We also followed 21,265 patients hospitalized for pernicious anemia in Sweden between 1965 and 1999 for an average of 7.1 years and estimated relative risks of esophageal cancer by histology. Finally, polymorphisms in *XPD* codon 751 (Lys→Gln) were genotyped and compared between cases and controls using material in the above-mentioned case-control study.

More than 6-fold and 14-fold excess risks for esophageal adenocarcinonia were observed among unoperated and operated gastroesophageal reflux disease patients, respectively. The risk among operated patients remained elevated regardless of time after surgery. We found a significantly reduced risk for esophageal adenocarcinoma associated with *H. pylori* infection. The inverse association remained in the stratum without stomach atrophy. In contrast. subjects with CagA positive serology had an about 2-fold excess risk for esophageal squamous-cell carcinoma. Compared with the general population, a significant excess risk for esophageal squamous-cell carcinoma was observed in pernicious anemia patients, while no significant risk elevation or reduction was observed for esophageal adenocarcinoma. *XPD* codon 751 Lys/Gln and Gln/Gln genotypes, compared with Lys/Lys genotype, were both associated with a more than doubled risk for esophageal

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adenocarcinoma. The combined effects of these genotypes and symptomatic gastroesophageal reflux departed from additivity, but only with borderline significance.

Gastroesophageal reflux is strongly associated with the risk of esophageal adenocarcinoma. However, the high risk of developing esophageal adenocarcinoma remains after antireflux surgery as practiced in Sweden. The effects of earlier intervention against GERD need to be evaluated. Infection with *H. pylori* is inversely associated with risk of esophageal adenocarcinoma, but the hypothesized pathway via atrophy – reduced acid load in the esophagus appears unlikely. Gastric atrophy following infection with CagA+ strains of *H. pylori* or type A atrophic gastritis may increase the risk for esophageal squamous-cell carcinoma. *XPD* 75lGln allele is a potential genetic marker for susceptibility to esophageal adenocarcinoma, and may interact multiplicatively with gastroesophageal reflux on the carcinogenesis of this tumor.

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Radon in natural waters—Analytical methods—Correlation to environmental parameters–radiation dose estimation–and GIS applications

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Investigations of radon in natural water and its relation to physical and chemical parameters are outlined in this thesis. In particular, a method for measuring ^{222}Rn in water at low concentrations (~ 20 $mBq \cdot l^{-1}$) is described, followed by discussions concerning the design and its application to study both radon and parameters influencing radon levels in natural waters. A topic considered is the impact of fluoride and other aquatic parameters on radon in water. Moreover, variables such as uranium series radionuclides and stable elements in water, bedrock and sediment radioactivity and geology are investigated in two case studies. This was performed by employing radiometric, chemical, statistical and GIS & geostatistical analyses. The general water chemistry and presence of some elements such as fluoride was observed to influence radon levels in water. Health aspects of radon in drinking water are discussed based on radiation dose assessments. The radiation doses are compared with and added to doses incurred from ingestion of uranium, radium and polonium isotopes in drinking water and inhalation of radon in air in order to estimate total exposures for different age categories. The results may have a potential for future epidemiologieal studies.

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