unclear. Induction of p27 in human K562 cells results in erythroid differentiation as well as CDK inhibition, RB hypo-phosphorylation and G1 arrest. We have studied the involvement of MYC in the p27-induced differentiation using K562 cells with conditional expression of p27 (inducible by zinc cations) and MYC (activable by 4-hydroxy-tamoxifen). In this model, activation of MYC inhibits the p27-mediated erythroid differentiation without reversing the cell cycle arrest imposed by p27. Microarray analysis revealed that, in the presence of p27, MYC blocked the up-regulation of several erythroid-specific genes, including GATA1 and NFE2, two transcriptions factors with a pivotal role in erythropoiesis. Co-transfection experiments show that MYC inhibits p27-induced differentiation, at least in part, through GATA1 down-regulation. In conclusion, we demonstrate a mechanism for MYC-mediated inhibition of differentiation depending on specific gene regulation and that can be separated from cell cycle effects. We hypothesize that this proliferation-independent differentiation inhibitory activity may be important for MYC-induced tumorigenesis.

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The modulation of protein synthesis by T3 in Caco-2 colorectal cancer cells - the role of nuclear targeting of TR receptors

T. Kantola[1], K. Tuppurainen[1], T. Hörkkö[1], T.J. Karttunen[1], S. Eskelinen[1], M.J. Mäkinen[1]
[1]University of Oulu, Pathology, Oulu, Finland

Introduction: Thyroid hormones, mainly T3, regulate growth, development, differentiation and metabolic processes in target tissues including intestinal mucosa. The actions of T3 are exerted through thyroid hormone receptors (TR), which belong to the nuclear steroid hormone receptor family. We have recently found decreased expression of TRβ1 in colorectal cancer. The effect of thyroid hormones on the growth on intestinal epithelial cells has not been studied.

Materials and methods: The effect of various concentrations of T3 on Caco-2 cell growth was studied. Cell growth was assessed with leucine incorporation, three-dimensional (3D) culture and by quantifying cell proliferation and apoptosis levels. TRα1, TRβ1 and β-catenin expression in nuclear and cytoplasmic fractions was assessed by Western blot analysis completed with immunohistochemistry and immunofluorescence.

Results: T3 limited cell growth and decreased protein synthesis in Caco-2 cells, induced nuclear targeting of TRα1 and TRβ1, but had no effect on β-catenin localization, except weaker membranous immunoreaction was observed in areas of evident nuclear translocation of TRα1 and TRβ1. In 3D culture, T3 induced differentiation of Caco-2 cells grown in type I collagen gel.

Conclusions: T3 induces nuclear translocation of its receptors TRα1 and Trβ1, and thereby mediates proliferation, differentiation and apoptosis in Caco-2 cells. Loss of membranous β-catenin associated with nuclear localization of TRα1 and Trβ1 suggests a link between Wnt and TR signaling pathways. All these findings suggest that disturbances in T3 signaling pathways could be involved in colorectal carcinogenesis.

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Expression of Aurora kinases in clear cell renal carcinoma

B. Martin[1], F. Jouan[1], N. Stock[1], J.G. Delcros[1,2], N. Rioux[1], J.J. Patard[1], J. Arlot[1], P. Fergelot[1,3]
[1]CNRS UMR 6061 "IGDR" IFR 140 G.F.A.S., Faculté de Médecine, Université Rennes 1, Rennes, France; [2] CNRS UMR 5238 - Laboratoire Apoptose, Cancer et Développement, Centre Léon Bérard, Lyon, France; [3] CHU Bordeaux, Service de Génétique médicale, Université V. Segalen Bordeaux 2, Bordeaux, France

Chromosome aberration is a hallmark of cancer cells. During mitosis, replicated chromosomes need to be equally distributed between the two daughter cells since errors at this stage can lead to aneuploïd cells and initiate cancerous transformation. Aurora protein kinases (A, B and C) have an important role in the progression of mitosis. They are involved in the formation and stability of the mitotic spindle and in cytokinesis. These kinases were described over-expressed in different cancers, leading to the development of inhibitors for these kinases.

A study of the transcriptional and translational expression of the Aurora kinases was initiated in clear cell renal carcinomas (CCRC). These tumours have been shown to be frequently mutated or inactivated for the suppressor of tumour Von-Hippel Lindau gene (VHL). Identification of new potential targets in CCRC which are resistant to most current treatments would allow the development of new anticancerous strategies.

The expression of the Aurora kinases was studied by RT-PCR, Western-blot and immunohistochemistry in tumour versus normal tissues. Aurora A and B transcripts were detected in tumour and normal tissues. In contrast, the Aurora C kinase was not expressed in normal nor in tumour tissues. High levels of Aurora-A kinase transcripts in the tumour were correlated with a bad prognosis and the presence of metastases. However, the amount of Aurora-A protein was always higher in normal kidney tissues than in the corresponding tumours, independently of the tumour stage. Discrepancies between the transcriptional and translational expression of the Aurora-A kinase in CCRC will be discussed.

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Investigating the roles of gelsolin in the malignant progression of colorectal tumor cells

E.H. Tan[1], B. Yan[2], S.C. Hooi[1], M. Salto-Tellez[2], C. Yap[1]
[1]National University of Singapore, Physiology, Singapore, Singapore; [2] National University Hospital, Pathology, Singapore, Singapore

Purpose of study: To investigate the role of gelsolin in the malignant progression of colorectal tumor cells.

Materials and Methods: A metastatic cell line (E1) was previously derived from the poorly metastatic human colorectal cancer cell line, HCT116, and exhibits a mesenchymal phenotype with enhanced migration. We studied the influence of gelsolin in progressive transformation of colorectal tumour cells using the E1/HCT116 in vitro model, as well as matched tumor samples from 13 patients.

Results: Compared to HCT116, gelsolin is upregulated in metastatic E1 cells. Knock down of gelsolin expression in E1 cells by siRNA to levels lower than in HCT116 increased fibronectin expression compared to control E1 and HCT116 cells. Immunohistochemical studies on samples derived from 13 colorectal cancer patients with liver metastases showed that gelsolin was reduced in the majority of both primary and metastatic tumours. However, gelsolin appeared to be upregulated at the invasive front of these tumors, consistent with the increased expression observed in metastatic E1 cells. Overexpression of gelsolin in pancreatic cancer cells increases cell motility (Thompson et al, 2007).

Conclusion: We postulate that gelsolin possibly enhances invasion and metastasis by affecting tumor cell migration, possibly by complex regulation of several migration-associated proteins.

Reference: Thompson, C.C., Ashcroft, F.J., Patel, S., Saraga, G., Vimalachandran, D., Prime, W., Campbell, F., Dodson, A., Jenkins, R.E., Lemoine, N.R., Crnogorac-Jurcevic, T., Yin, H.L., Costello, E. Pancreatic cancer cells overexpress gelsolin family-capping proteins, which contribute to their cell motility (2007). Guy 56:95-106.

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Estrogen receptor beta and the progression of prostate cancer - role of 5alpha-androstane-3beta,17beta-diol (3beta-Adiol)

D. Dondi[1], M. Piccolella[1], P. Ciana[2], A. Maggi[2], A. Locatelli[1], M. Motta[1], D. Sau[1], A. Poletti[1]
[1]University of Milano, Department of Endocrinology, Milano, Italy; [2] University of Milano, Department of Pharmacological Sciences, Milano, Italy

Introduction: Prostate cancer (PC) develops in response to an abnormal activation of androgen receptor by circulating androgens and it is pharmacologically controlled by androgen blockade. However, androgen-ablation therapy often correlates with the growth of androgen-independent PC and increased invasiveness. Recently, we found that the testosterone derivative dihydrotestosterone (DHT) inhibits PC cell migration through the conversion to its metabolite 5alpha-androstane-3beta,17beta-diol (3beta-Adiol), which is unable to bind AR, but interacts with the estrogen receptor beta (ERbeta).

Methods and Results: To further investigate the role of 3beta-Adiol in PC progression, we performed in vitro growth and invasion studies on human PC3 cells prostate cancer cells. Thymidine incorporation experiments demonstrated that a dose-dependent decrease in cell proliferation was observed in PC3 treated with 3beta-Adiol for 48 h; on the contrary, estradiol treatment was ineffective, suggesting the existence of different pathways for ERbeta activation in PC3 cells. A 3beta-Adiol treatment of PC3 cells seeded on laminin for 48 h leaded to a significant decrease in cell detachment with respect to untreated cells. Moreover, 3beta-Adiol-treated PC3 cells showed a significant decrease in invasive capacity as measured by the invasion of reconstituted basement membrane (Matrigel).

Finally, we performed in vivo experiments by using a PC-3 orthotopic model with bioluminescence imaging as an end point. PC-3 cells stably expressing the luciferase gene were surgically implanted into the prostates of male nude mice. Mice were given subcutaneous doses of 3beta-Adiol (75 mg/kg) for 15 days. Mice were then imaged twice a week for 2 weeks with a Xenogen system. A significant decrease of prostate tumours was observed in the orthotopic animal model treated with 3beta-Adiol with respect to untreated animals.

Conclusions: These data show that 3beta-Adiol is an effective agent against human prostate cancer development and that the estrogenic effect of testosterone derivatives (ERbeta-dependent) inhibits not only cell migration, but also invasion and may be protective against PC invasion and metastasis.