17beta-hydroxysteroid dehydrogenase type 1 is an independent prognostic marker in breast cancer.

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Author: Olayiwola O Oduwole
Yan Li
Veli V Isomaa
Anne Mäntyniemi
Anitta E Pulkka
Ylermi Soini
Pirkko T Vihko

Author Affiliation: Biocenter Oulu and Research Center for Molecular Endocrinology, WHO Collaborating Centre for Research on Reproductive Health, Oulu, Finland.

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Ki-67 Antigen - biosynthesis - genetics
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RNA, Messenger - biosynthesis - genetics
Receptor, erbB-2 - biosynthesis - genetics
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Tumor Markers, Biological - biosynthesis - genetics
Abstract: Estrogens have an important role in the development and progression of breast cancer. 17beta-Hydroxysteroid dehydrogenase type 1 (17HSD1), type 2 (17HSD2), and type 5 (17HSD5) are associated with sex steroid metabolism in normal and cancerous breast tissue. The mRNA expressions of the 17HSD1, 17HSD2, and 17HSD5 enzymes were analyzed in 794 breast carcinoma specimens by using tissue microarrays and normal histologic sections. The results were correlated with the estrogen receptor alpha (ER-alpha) and beta (ER-beta), progesterone receptor, Ki67, and c-erbB-2 expressions analyzed by immunohistochemical techniques and with the Tumor-Node-Metastasis classification, tumor grade, disease-free interval, and survival of the patients. Signals for 17HSD1 mRNA were detected in 16%, 17HSD2 in 25%, and 17HSD5 in 65% of the breast cancer specimens. No association between the 17HSD1, 17HSD2, and 17HSD5 expressions was detected. A significant association was observed between ER-alpha and ER-beta (P = 0.02; odds ratio, 1.96) expressions. There was also a significant inverse association between ER-alpha and 17HSD1 (P = 0.04; odds ratio, 0.53), as well as ER-alpha and 17HSD5 (P = 0.001; odds ratio, 0.35). Patients with tumors expressing 17HSD1 mRNA or protein had significantly shorter overall and disease-free survival than the other patients (P = 0.0010 and 0.0134, log rank). The expression of 17HSD5 was significantly higher in breast tumor specimens than in normal tissue (P = 0.033; odds ratio, 5.56). The group with 17HSD5 overexpression had a worse prognosis than the other patients (P = 0.0146). ER-alpha also associated with survival (P = 0.045). Cox multivariate analyses showed that 17HSD1 mRNA, tumor size, and ER-alpha had independent prognostic significance.

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17Beta-hydroxysteroid dehydrogenase type 2: independent prognostic significance and evidence of estrogen protection in female patients with colon cancer.

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Author: Olayiwola O Oduwole
Markus J Mäkinen
Veli V Isomaa
Anitta Pulkka
Petra Jernvall
Tuomo J Karttunen
Pirkko T Vihko

Author Affiliation: Biocenter Oulu, Research Center for Molecular Endocrinology, WHO Collaborating Centre for Research on Reproductive Health, P.O. Box 5000, University of Oulu, FIN-90014 Oulu, Finland.


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Abstract:
The mRNA expression of 17beta-hydroxysteroid dehydrogenase (17HSD) types 1 and 2 enzymes catalyzing opposite reaction of estrogen metabolism was investigated in colon cancer. Further, the significance of the 17HSD type 2 enzyme as a possible marker of colorectal cancer (CRC) prognosis was studied. In the normal mucosa, 17HSD type 2 mRNA was predominantly expressed in the surface epithelium and in the upper parts of the crypts. In the lamina propria expression was seen in endothelial cells and mononuclear phagocytes. In colorectal tumors, 17HSD type 2 expression was in most cases downregulated. Female patients had significantly more cancers with high 17HSD type 2 mRNA expression (n=11/35; 31%) than male patients (n=3/39; 8%) (P=0.02). We observed a significant impact of 17HSD type 2 mRNA expression on survival in female patients with distal colorectal cancer (n=24), with an overall cumulative 5-year survival rate of 54% in those with low 17HSD type 2 mRNA expression. None of the female patients with high 17HSD type 2 mRNA expression survived (n=11; P=0.0068; log rank 7.32). In male patients, no significant association with survival was observed. Our data provide evidence suggesting that low 17HSD type 2 mRNA expression is an independent marker of favorable prognosis in females with distal colorectal cancer, supporting the presence of gender- and location-related differences in the pathogenesis of colon cancer.

PubMed ID: 14672733 View in PubMed
Abstract: Familial hypercholesterolemia (FH) is seen with high frequency in the province of Québec, Canada. A large deletion (> 10 kb) of the 5'-end of the low density lipoprotein receptor (LDL-R) gene is the major mutation of the LDL-R in FH subjects in Québec (approximately 60% of FH subjects). No mRNA is produced from the allele bearing the mutation, and cellular cholesterol obtained by receptor-mediated endocytosis is under the control of the non-deletion allele. We have previously reported that some patients with the 10-kb deletion (approximately 9%) fail to respond to the hydroxymethylglutaryl coenzyme A reductase (HMG CoA reductase) inhibitor class of medications. We studied mRNA levels of the LDL-R and HMG CoA reductase genes in response to the HMG CoA reductase inhibitor lovastatin in a time- and dose-dependent fashion in cultured human skin fibroblasts and we devised an in vitro model to study the response to drug therapy in subjects with FH. We determined mRNA levels by RNase protection assay in skin fibroblasts obtained from controls (n = 3) and FH subjects with the > 10-kb deletion (responders, n = 3; non-responders, n = 3; to drug therapy). We measured 125I-LDL binding on skin fibroblasts grown in the presence of lipoprotein-deficient serum with or without 1 microMLovastatin, using 10 micrograms/mL of 125I-LDL protein. Control subjects exhibited coordinate regulation of the LDL-R and HMG CoA reductase genes in response to lovastatin, 0.1-25 microM, for 0-24 h. Correlation coefficients between mRNA levels of both genes were > 0.9 in controls and FH subjects. However, by linear regression analysis, the corresponding slopes for the correlation between both genes were 0.98 (controls), 3.36 and 3.63 (FH responders and non-responders), indicating a pattern of dissociated but still coordinate regulation in FH subjects. The magnitude of increase of mRNA levels of the LDL-R gene was approximately five-fold over LPDS in controls, two-fold in FH responders and two-fold in non-responders. Binding studies using 125I-LDL reveal that a control subject and all responders had a 2-2.5-fold increase in binding to cell surface receptors but two out of three FH non-responders showed no increase in binding in response to 1 microMlovastatin. The LDL-R and HMG CoA reductase genes are expressed in coordinate regulation in fibroblasts from subjects with FH due to the > 10-kb deletion, but with a proportionately greater up-regulation of the HMG CoA reductase gene. Some subjects, with FH caused by the > 10-kb deletion of the LDL-R gene, who fail to respond to HMG CoA reductase inhibitors have abnormal LDL receptor binding activity at the cell surface in response to lovastatin in vitro.

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The anti-inflammatory action of methotrexate is not mediated by lymphocyte apoptosis, but by the suppression of activation and adhesion molecules.

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Author: Andrew Johnston
Johann Eli Gudjonsson
Hekla Sigmundsdottir
Björn Runar Ludviksson
Helgi Valdimarsson

Author Affiliation: Department of Immunology, Landspitali University Hospital, 101 Reykjavik, Iceland.


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Low-dose methotrexate (MTX) is an established and highly effective treatment for severe psoriasis and rheumatoid arthritis; however, its mechanism of action remains unclear. We investigated the effects of low-dose MTX on antigen-stimulated peripheral blood mononuclear cells and explored through which cellular pathways these effects are mediated. We show that MTX caused a dose-dependent suppression of T cell activation and adhesion molecule expression, and this was not due to lymphocyte apoptosis. The suppression of intercellular adhesion molecule (ICAM)-1 was adenosine and folate-dependent, while MTX suppression of the skin-homing cutaneous lymphocyte-associated antigen (CLA) was adenosine-independent. The effect of MTX on CLA, but not ICAM-1, required the constant presence of MTX in cultures. Thus, the suppression of T cell activation and T cell adhesion molecule expression, rather than apoptosis, mediated in part by adenosine or polyglutamated MTX or both, are important mechanisms in the anti-inflammatory action of MTX.

15639649 View in PubMed

Availability of in vitro vitellogenin assay for screening of estrogenic and anti-estrogenic activities of environmental chemicals.

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Author:
Iguchi Taisen
Irie Fumi
Urushitani Hiroshi
Tooi Osamu
Kawashima Yukio
Roberts Mike
Norrgren Leif
Hutchinson Thomas
Vitellogenin (VTG) protein, VTG mRNA, other egg yolk proteins, vitelline envelope proteins and their mRNAs are produced in the liver of oviparous species by stimulation of endogenous estrogen and exogenous estrogenic chemicals. The VTG assay based on enzyme-linked immunosorbent assay (ELISA) has been widely used for many fish species to screen estrogenic and anti-estrogenic activities of chemicals and sewage effluents using immature fish and/or male fish. In order to reduce the number of fish for screening of estrogenicity and anti-estrogenicity of chemicals, primary cultured fish hepatocytes can be used. In fact, primary cultured hepatocytes have been successfully used for the detection of estrogenic and anti-estrogenic activities of environmental chemicals in selected OECD fish species, e.g., medaka (Oryzias latipes) and rainbow trout (Oncorhynchus mykiss) together with other fish species such as Atlantic salmon (Salmo salar L.), Siberian sturgeon (Acipenser baeri), tilapia (Oreochromis mossambicus), carp (Cyprinus carpio), bream (Abramis brama), Carassius auratus, silver eel (Anguilla anguilla L.), and channel catfish (Ictalurus punctatus). In terms of hepatocyte assays relating to other taxa, these include frogs such as Xenopus laevis and the common green frog (Rana esculenta), chickens (Gallus domesticus) and herring gulls (Larus argentatus). VTG mRNA measurement by quantitative reverse transcription-polymerase chain reaction has also been successfully applied in the primary cultured hepatocytes of various species.

Cathepsins in human obesity: changes in energy balance predominantly affect cathepsins in adipose tissue and in circulation.

https://arctichealth.org/en/permalink/ahliterature145342
Abstract:
Recent studies in humans and mice suggest the implication of the cysteine proteases cathepsins S, L, and K in vascular and metabolic complications of obesity.

Our objective was to identify clinically relevant forms of cathepsin in human obesity.

We conducted a prospective study on two independent cohorts.

The first cohort includes 45 obese women eligible for gastric surgery (age, 39 +/- 1.6 yr; body mass index, 47 +/- 0.99 kg/m(2)) and 17 nonobese women (age, 38 +/- 1.8 yr; body mass index, 21 +/- 0.44 kg/m(2)). The second cohort comprises 29 obese women (age, 57 +/- 0.8 yr; body mass index, 34 +/- 0.69 kg/m(2)) undergoing 6 months of medically supervised caloric restriction.

Cathepsin S, L, and K mRNA levels were determined in surgical adipose tissue biopsies. The proteins were measured in conditioned medium of adipose tissue explants and in circulation.

Obese subjects had a 2-fold increase in cathepsin S mRNA in adipose tissue as compared with normal-weight subjects and an increased rate (1.5-fold) of cathepsin S release in adipose tissue explants. Cathepsin S circulating concentrations were increased with obesity (+30%) and reduced after weight reduction (P

PubMed ID: 20164293 View in PubMed
A comparison of gene expression profiles in different types of human brain tumours and normal brain by Serial Analysis of Gene Expression (SAGE) revealed exceptionally high content of CTTGGGTTTT tag in meningioma and ependymoma SAGE-libraries. A search of the most relevant gene for this tag on the website "SAGE Anatomic Viewer" showed that it belonged to the nucleotide sequence of insulin-like growth factor II (IGF-II) gene as well as to the open reading frame 43 on a chromosome 11 (C11orf43). This nucleotide sequence encodes putative insulin-like growth factor II associated protein (IGF-IIA). mRNA for this protein is produced as a result of the processing of IGF-II gene primary transcript. Northern analysis of glial tumours and meningiomas showed the exceptionally high level of mRNA of IGF-II-associated protein in meningiomas. Protein, encoded by this mRNA, can play the important role in meningioma formation and may be used as their specific molecular marker.
In this study we investigated the immunohistochemical expression of inducible nitric oxide synthase (iNOS) in a set of normal pleural mesothelial tissues, malignant mesotheliomas, mesothelioma cell lines and metastatic pleural adenocarcinomas. Furthermore, the expression of mRNA was assessed in four malignant mesothelioma cell lines in culture. Apoptosis and vascular density in malignant mesotheliomas was assessed by the TUNEL method and by immunohistochemistry with an antibody against FVIII-related antigen. Immunohistochemically mesothelial cells in non-neoplastic healthy pleural tissues were mostly negative for iNOS. Positivity for iNOS was observed in 28/38 (74%) and 24/25 (96%) of malignant mesotheliomas and metastatic pleural adenocarcinomas, respectively. Epithelial and mixed mesotheliomas expressed more often strong iNOS immunoreactivity compared to the sarcomatoid subtype (P = 0.023). Moreover, metastatic adenocarcinomas expressed more often iNOS positivity than mesotheliomas (P = 0.021). Experiments with the cell lines confirmed that malignant mesothelioma cells are capable of synthesizing iNOS. No significant association was found between iNOS expression and apoptosis or vascular density in malignant mesotheliomas. The higher expression of iNOS in the epithelial subtype of mesothelioma and pleural metastatic adenocarcinoma might be due to an increased sensitivity of these cell types to cytokine-mediated iNOS upregulation. The strong expression of iNOS suggests a putative role for NO in the growth and progression of these tumours.
Expression of mRNAs for type I and type III procollagens in serous ovarian cystadenomas and cystadenocarcinomas.

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Author: S. Kauppila
J. Saarela
F. Stenbäck
J. Risteli
A. Kauppila
L. Risteli

Author Affiliation: Department of Medical Biochemistry, University of Oulu, Finland.


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Cystadenoma, Serous - metabolism - pathology
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Procollagen - biosynthesis - genetics
RNA Probes
RNA, Messenger - biosynthesis - genetics
RNA, Neoplasm - biosynthesis - genetics
Research Support, Non-U.S. Gov't

Abstract: Malignant ovarian tumors induce a strong fibro-proliferative reaction characterized by the active production of type I and type III procollagen both locally in the ovary as well as more remotely in the peritoneal cavity. Our purpose was to determine the origin of the increased collagen production observed in serous ovarian tumors with different histological grades of malignancy, ie, whether the malignant cells or the stromal fibroblasts are responsible for the synthesis of collagen fibers. We visualized the mRNAs corresponding to the pro alpha 1(I) and pro alpha 2(I) chains of type I procollagen and the pro alpha 1(III) chain of type III procollagen by in situ hybridization. Strong signals for both chains of type I procollagen were seen in stromal fibroblasts next to tumor cell islets, whereas the reaction was weak or absent near benign ovarian cysts. In poorly differentiated tumors, the signals were particularly abundant and occasionally also seen in the neoplastic cells themselves. Type III procollagen mRNA expression was similar, although somewhat less distinct. These findings indicate that the production of interstitial procollagens is related to the degree of malignancy and neoplastic activity of tumors. The formation of collagen in well differentiated ovarian tumors is a function of stromal fibroblasts, whereas in poorly differentiated tumors, aberrant expression of one or several chains of type I and type III procollagens in the neoplastic cells is also likely to take place.

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Four novel mutations in deficiency of coagulation factor XIII: consequences to expression and structure
of the A-subunit.

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Author: H. Mikkola
        V C Yee
        M. Syrjälä
        R. Seitz
        R. Egbring
        P. Petrini
        R. Ljung
        J. Ingerslev
        D C Teller
        L. Peltonen
        A. Palotie

Author Affiliation: Department of Clinical Chemistry, University of Helsinki, Finland.

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Abstract:
The characterization of naturally occurring mutations is one way to approach functionally significant domains of polypeptides. About 10 mutations have been reported in factor XIII (FXIII) A-subunit deficiency, but very little is known about the effects of the mutations on the expression or the structure of this enzyme. In this study, the recent crystallization of FXIII A-subunit and determination of the three-dimensional model were used for the first time to pursue the structural consequences of mutations in the A-subunit. The molecular analysis of four families from Sweden, Germany, and Denmark revealed four previously unreported point mutations. Three of the mutations were missense mutations, Arg326-->Gln, Arg252-->Ile, and Leu498-->Pro, and one was a nonsense mutation, a deletion of thymidine in codon for Phe8 resulting in early frameshift and premature termination of the polypeptide chain. In the case of the nonsense mutation, delT Phe8, the steady-state mRNA level of FXIII A-subunit was reduced, as quantitated by reverse transcriptase-polymerase chain reaction and solid-phase minisequencing. In contrast, none of the missense mutations affected mRNA levels, indicating the possible translation of the mutant polypeptides. However, by enzyme-linked immunosorbent analysis and immunofluorescence, all the patients demonstrated a complete lack of detectable factor XIII A antigen in their platelets. In the structural analysis, we included the mutations described in this work and the Met242-->Thr mutation reported earlier by us. Interestingly, in the three-dimensional model, all four missense mutations are localized in the evolutionarily conserved catalytic core domain. The substitutions are at least 15 A away from the catalytic cleft and do not affect any of the residues known to be directly involved in the enzymatic reaction. The structural analyses suggest that the mutations are most likely interfering with proper folding and stability of the protein, which is in agreement with the observed absence of detectable FXIII A antigen. Arg326, Arg252, and Met242 are all buried within the molecule. The Arg326-->Gln and Arg252-->Ile mutations are substitutions of smaller, neutral amino acids for large, charged residues. They disrupt the electrostatic balance and hydrogen-bonding interactions in structurally significant areas. The Met242-->Thr mutation is located in the same region of the core domain as the Arg252-->Ile site and is expected to have a destabilizing effect due to an introduction of a smaller, polar residue in a tightly packed hydrophobic pocket. The substitution of proline for Leu498 is predicted to cause unfavorable interatomic contacts and a disruption of the alpha-helix mainchain hydrogen-bonding pattern; it is likely to form a kink in the helix next to the dimer interface and is expected to impair proper dimerization of the A-subunits. In the case of all four missense mutations studied, the knowledge achieved from the three-dimensional model of crystallized FXIII A-subunit provides essential information about the structural significance of the specific residues and aids in understanding the biologic consequences of the mutations observed at the cellular level.

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