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Evolution and function of vitamin D.

[Enlace de documentos de ProQuest](#)

Resumen: It is remarkable that phytoplankton and zooplankton have been producing vitamin D for more than 500 million years. The role of vitamin D in lower non-vertebrate life forms is not well understood. However, it is critically important that most vertebrates obtain an adequate source of vitamin D, either from exposure to sunlight or from their diet, in order to develop and maintain a healthy mineralized skeleton. Vitamin D deficiency is an unrecognized epidemic in most adults who are not exposed to adequate sunlight. This can precipitate and exacerbate osteoporosis and cause the painful bone disease osteomalacia. Once vitamin D is absorbed from the diet or made in the skin by the action of sunlight, it is metabolized in the liver to 25-hydroxyvitamin D [25(OH)D] and then in the kidney to 1,25-dihydroxyvitamin D [1,25(OH)2D]. 1,25(OH)2D interacts with its nuclear receptor (VDR) in the intestine and bone in order to maintain calcium homeostasis. The VDR is also present in a wide variety of other tissues. 1,25(OH)2D interacts with these receptors to have a multitude of important physiological effects. In addition, it is now recognized that many tissues, including colon, breast and prostate, have the enzymatic machinery to produce 1,25(OH)2D. The insights into the new biological functions of 1,25(OH)2D in regulating cell growth, modulating the immune system and modulating the renin-angiotensin system provides an explanation for why diminished sun exposure at higher latitudes is associated with increased risk of dying of many common cancers, developing type 1 diabetes and multiple sclerosis, and having a higher incidence of hypertension. Another calciotropic hormone that is also produced in the skin, parathyroid hormone-related peptide, is also a potent inhibitor of squamous cell proliferation. The use of agonists and antagonists for PTHrP has important clinical applications for the prevention and treatment of skin diseases and disorders of hair growth.

Materia: Index Medicus; Space life sciences;

Materia de MeSH: Animals; Humans; Evolution, Chemical (principal); Vitamin D -- physiology (principal)

Sustancia: Sustancia: Vitamin D; CAS: 1406-16-2;

Título: Evolution and function of vitamin D.

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Documento 2 de 4

Analysis of the vitamin D system in cutaneous malignancies.

[Enlace de documentos de ProQuest](#)

Resumen: 1,25-dihydroxyvitamin D₃, the biological active metabolite of vitamin D, has great impact on keratinocyte growth and differentiation, and consequently has already been successfully used in the therapy of hyperproliferative skin disorders. We have now characterized the key components of the vitamin D system (VDR, 1 α -OHase, 24-OHase and 25-OHase) in cutaneous basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), using immunohistochemical and quantitative real-time PCR techniques. Additionally, proliferative activity (Ki-67 expression), differentiation status (cytokeratin 10 and transglutaminase K expression), rate of apoptosis (TUNEL assay) and the abundance of the main heterodimerization partners of VDR (RXRs) was determined for these tumours and correlated with the components of the Vitamin D system. Our findings indicate that the Vitamin D system may be of high importance for the growth behaviour of BCCs and SCCs and that new vitamin D analogues that exert less calcaemic side effects may be effective in the prevention or treatment of these tumours.

Materia: Index Medicus; Space life sciences;

Materia de MeSH: Case-Control Studies; DNA Primers -- chemistry; Gene Expression; Humans; Immunoenzyme Techniques; In Situ Nick-End Labeling; Ki-67 Antigen -- metabolism; Neoplasm Proteins -- metabolism; Polymerase Chain Reaction; RNA, Messenger -- genetics; RNA, Messenger -- metabolism; RNA, Neoplasm -- genetics; RNA, Neoplasm -- metabolism; Receptors, Retinoic Acid -- genetics; Receptors, Retinoic Acid -- metabolism; Transglutaminases -- analysis; 25-Hydroxyvitamin D₃ 1- α -Hydroxylase -- genetics; 25-Hydroxyvitamin D₃ 1- α -Hydroxylase -- metabolism (principal); Carcinoma, Basal Cell -- enzymology (principal); Carcinoma, Basal Cell -- genetics; Carcinoma, Squamous Cell -- enzymology (principal); Carcinoma, Squamous Cell -- genetics; Cytochrome P-450 Enzyme System -- genetics; Cytochrome P-450 Enzyme System -- metabolism (principal); Receptors, Calcitriol -- genetics; Receptors, Calcitriol -- metabolism (principal); Skin

Neoplasms -- enzymology (principal); Skin Neoplasms -- genetics; Steroid Hydroxylases -- genetics; Steroid Hydroxylases -- metabolism (principal)

Sustancia: Sustancia: DNA Primers; CAS: 0; Sustancia: Ki-67 Antigen; CAS: 0; Sustancia: Neoplasm Proteins ; CAS: 0; Sustancia: RNA, Messenger; CAS: 0; Sustancia: RNA, Neoplasm; CAS: 0; Sustancia: Receptors, Calcitriol; CAS: 0; Sustancia: Receptors, Retinoic Acid; CAS: 0; Sustancia: Cytochrome P-450 Enzyme System; CAS: 9035-51-2; Sustancia: 25-Hydroxyvitamin D3 1-alpha-Hydroxylase; CAS: EC 1.14.-; Sustancia: Steroid Hydroxylases; CAS: EC 1.14.-; Sustancia: vitamin D 24-hydroxylase; CAS: EC 1.14.13.126; Sustancia: Transglutaminases; CAS: EC 2.3.2.13;

Título: Analysis of the vitamin D system in cutaneous malignancies.

Autor: Kamradt, Jörn¹ ; Rafi, Leyla; Mitschele, Tanja; Meineke, Viktor; Gärtner, Barbara C; Wolfgang, Tilgen; Holick, Michael F; Reichrath, Jörg¹ Department of Dermatology, University of Saarland, Kirrberger Str., 66421 Homburg/Saar, Germany.

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X-ray structure of the hRORalpha LBD at 1.63 Å: structural and functional data that cholesterol or a cholesterol derivative is the natural ligand of RORalpha.

[Enlace de documentos de ProQuest](#)

Resumen: The retinoic acid-related orphan receptor alpha (RORalpha) is an orphan member of the subfamily 1 of nuclear hormone receptors. No X-ray structure of RORalpha has been described so far, and no ligand has been identified. We describe the first crystal structure of the ligand binding domain (LBD) of RORalpha, at 1.63 Å resolution. This structure revealed a ligand present in the ligand binding pocket (LBP), which was identified by X-ray crystallography as cholest-5-en-3beta-ol (cholesterol). Moreover, RORalpha transcriptional activity could be modulated by changes in intracellular cholesterol level or mutation of residues involved in cholesterol binding. These findings suggest that RORalpha could play a key role in the regulation of cholesterol homeostasis and thus represents an important drug target in cholesterol-related diseases.

Materia: Index Medicus;

Materia de MeSH: Crystallography, X-Ray; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors -- pharmacology; Ligands; Lovastatin -- pharmacology; Nuclear Receptor Subfamily 1, Group F, Member 1; Protein Conformation; Spectrometry, Mass, Electrospray Ionization; Transcription, Genetic -- drug effects; Transcription, Genetic -- physiology; Tumor Cells, Cultured; Cholesterol -- metabolism (principal); Receptors, Cytoplasmic and Nuclear -- chemistry (principal); Receptors, Cytoplasmic and Nuclear -- metabolism; Receptors, Cytoplasmic and Nuclear -- physiology; Trans-Activators -- chemistry (principal); Trans-Activators -- metabolism; Trans-Activators -- physiology

Sustancia: Sustancia: Hydroxymethylglutaryl-CoA Reductase Inhibitors; CAS: 0; Sustancia: Ligands; CAS: 0; Sustancia: Nuclear Receptor Subfamily 1, Group F, Member 1; CAS: 0; Sustancia: RORA protein, human; CAS: 0; Sustancia: Receptors, Cytoplasmic and Nuclear; CAS: 0; Sustancia: Trans-Activators; CAS: 0; Sustancia: Cholesterol; CAS: 97C5T2UQ7J; Sustancia: Lovastatin; CAS: 9LHU78OQFD;

Secuencia genética: Secuencia: 1N83; Banco de datos: PDB;

Título: X-ray structure of the hRORalpha LBD at 1.63 Å: structural and functional data that cholesterol or a cholesterol derivative is the natural ligand of RORalpha.

Autor: Kallen, Joerg A¹ ; Schlaeppi, Jean-Marc; Bitsch, Francis; Geisse, Sabine; Geiser, Martin; Delhon, Isabelle; Fournier, Brigitte¹ Central Technologies, Protein Structure Unit, Novartis Pharma AG, CH-4002 Basel, Switzerland. joerg.kallen@pharma.novartis.com

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Abreviatura de revista: Structure

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Documento 4 de 4

X-ray structure of the orphan nuclear receptor RORbeta ligand-binding domain in the active conformation.

[Enlace de documentos de ProQuest](#)

Resumen: The retinoic acid-related orphan receptor beta (RORbeta) exhibits a highly restricted neuronal-specific expression pattern in brain, retina and pineal gland. So far, neither a natural RORbeta target gene nor a functional ligand have been identified, and the physiological role of the receptor is not well understood. We present the crystal structure of the ligand-binding domain (LBD) of RORbeta containing a bound stearate ligand and complexed with a coactivator peptide. In the crystal, the monomeric LBD adopts the canonical agonist-bound form. The fatty acid ligand-coactivator peptide combined action stabilizes the transcriptionally active conformation. The large ligand-binding pocket is strictly hydrophobic on the AF-2 side and more polar on the beta-sheet side where the carboxylate group of the ligand binds. Site-directed mutagenesis experiments validate the significance of the present structure. Homology modeling of the other isoforms will help to design isotype-selective agonists and antagonists that can be used to characterize the physiological functions of RORs. In addition, our crystallization strategy can be extended to other orphan nuclear receptors, providing a powerful tool to delineate their functions.

Materia: Index Medicus;

Materia de MeSH: Amino Acid Sequence; Animals; Binding Sites -- physiology; Crystallography, X-Ray; Histone Acetyltransferases; Ligands; Macromolecular Substances; Molecular Sequence Data; Mutagenesis, Site-Directed; Nuclear Receptor Coactivator 1; Nuclear Receptor Subfamily 1, Group F, Member 2; Protein Conformation; Protein Structure, Tertiary -- physiology; Rats; Sequence Alignment; Sequence Homology,

Amino Acid; Structure-Activity Relationship; Models, Molecular (principal); Peptide Fragments -- chemistry (principal); Peptide Fragments -- metabolism; Receptors, Cell Surface -- chemistry (principal); Receptors, Cell Surface -- physiology; Receptors, Cytoplasmic and Nuclear (principal); Stearic Acids -- chemistry (principal); Transcription Factors -- chemistry (principal)

Sustancia: Sustancia: Ligands; CAS: 0; Sustancia: Macromolecular Substances; CAS: 0; Sustancia: Nuclear Receptor Subfamily 1, Group F, Member 2; CAS: 0; Sustancia: Peptide Fragments; CAS: 0; Sustancia: Receptors, Cell Surface; CAS: 0; Sustancia: Receptors, Cytoplasmic and Nuclear; CAS: 0; Sustancia: Stearic Acids; CAS: 0; Sustancia: Transcription Factors; CAS: 0; Sustancia: stearic acid; CAS: 4ELV7Z65AP; Sustancia: Histone Acetyltransferases; CAS: EC 2.3.1.48; Sustancia: Nuclear Receptor Coactivator 1; CAS: EC 2.3.1.48;

Datos suplementarios: Cites: Nucleic Acids Res. 2000 Jan 1;28(1):235-42[10592235], Cites: Nat Struct Biol. 1999 May;6(5):458-63[10331874], Cites: Mol Cell. 2000 Jan;5(1):173-9[10678179], Cites: J Med Chem. 2000 Feb 24;43(4):527-50[10691680], Cites: Mol Endocrinol. 2000 May;14(5):700-17[10809233], Cites: Proc Natl Acad Sci U S A. 2000 Jun 20;97(13):7160-5[10860982], Cites: Mol Cell. 2000 Feb;5(2):289-98[10882070], Cites: Proc Natl Acad Sci U S A. 2000 Aug 1;97(16):9197-202[10900268], Cites: Acta Crystallogr D Biol Crystallogr. 2000 Jul;56(Pt 7):933-5[10930850], Cites: J Biol Chem. 2000 Sep 1;275(35):27045-54[10854433], Cites: Proc Natl Acad Sci U S A. 2000 Aug 29;97(18):10132-7[10963675], Cites: J Biol Chem. 2000 Oct 6;275(40):30749-52[10934217], Cites: J Neurochem. 2000 Dec;75(6):2392-400[11080190], Cites: Science. 2000 Dec 15;290(5499):2140-4[11118147], Cites: Cell Mol Life Sci. 2000 Nov;57(12):1748-69[11130180], Cites: EMBO Rep. 2001 Jan;2(1):42-8[11252722], Cites: J Biol Chem. 2001 May 4;276(18):15059-65[11278577], Cites: Annu Rev Biophys Biomol Struct. 2001;30:329-59[11340063], Cites: J Biol Chem. 2001 Mar 9;276(10):7465-74[11053444], Cites: Science. 2001 Jun 22;292(5525):2329-33[11408620], Cites: Proc Natl Acad Sci U S A. 1989 Jul;86(14):5310-4[2546152], Cites: Acta Crystallogr A. 1991 Mar 1;47 (Pt 2):110-9[2025413], Cites: Cell. 1991 Jun 28;65(7):1255-66[1648450], Cites: Proc Natl Acad Sci U S A. 1992 Jul 1;89(13):6167-71[1631105], Cites: J Mol Graph. 1993 Jun;11(2):134-8, 127-8[8347566], Cites: Structure. 1994 Jun 15;2(6):523-34[7922029], Cites: Genes Dev. 1994 Mar 1;8(5):538-53[7926749], Cites: Mol Endocrinol. 1994 Jun;8(6):757-70[7935491], Cites: Biochem Biophys Res Commun. 1994 Dec 30;205(3):1976-83[7811290], Cites: Nature. 1995 Jun 1;375(6530):377-82[7760929], Cites: Science. 1995 Nov 24;270(5240):1354-7[7481822], Cites: Nature. 1995 Dec 14;378(6558):681-9[7501014], Cites: Nature. 1995 Dec 14;378(6558):690-7[7501015], Cites: Cell. 1995 Dec 15;83(6):835-9[8521507], Cites: Proc Natl Acad Sci U S A. 1995 Dec 19;92(26):12265-9[8618882], Cites: Nat Struct Biol. 1996 Jan;3(1):87-94[8548460], Cites: Protein Profile. 1995;2(11):1173-308[8681033], Cites: Proc Natl Acad Sci U S A. 1996 Sep 17;93(19):10105-10[8816759], Cites: J Biol Chem. 1997 Mar 14;272(11):7140-50[9054409], Cites: Nature. 1997 Jun 12;387(6634):677-84[9192892], Cites: Nature. 1997 Jun 12;387(6634):733-6[9192902], Cites: Genomics. 1997 Jul 1;43(1):78-84[9226375], Cites: Nature. 1997 Oct 16;389(6652):753-8[9338790], Cites: Endocrinology. 1998 May;139(5):2335-41[9564842], Cites: Curr Opin Cell Biol. 1998 Jun;10(3):373-83[9640539], Cites: EMBO J. 1998 Jul 15;17(14):3867-77[9670004], Cites: Nihon Rinsho. 1998 Jul;56(7):1729-33[9702045], Cites: Nature. 1998 Sep 10;395(6698):137-43[9744270], Cites: Acta Crystallogr D Biol Crystallogr. 1998 Sep 1;54(Pt 5):905-21[9757107], Cites: Genes Dev. 1998 Nov 1;12(21):3343-56[9808622], Cites: Cell. 1998 Dec 23;95(7):927-37[9875847], Cites: Mol Cell. 1999 Mar;3(3):397-403[10198642], Cites: Cell. 1999 Apr 16;97(2):161-3[10219237], Cites: Endocr Rev. 1999 Oct;20(5):689-725[10529899], Cites: Genes Dev. 2000 Jan 15;14(2):121-41[10652267]

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Autor: Stehlin, C¹ ; Wurtz, J M; Steinmetz, A; Greiner, E; Schüle, R; Moras, D; Renaud, J P¹ Laboratoire de Biologie et Génomique Structurales (CNRS Unité Propre de Recherche 9004), Institut de Génétique et de Biologie Moléculaire et Cellulaire (CNRS/INSERM/Université Louis Pasteur), 1 rue Laurent Fries, BP 163, 67404 Illkirch, France.

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