

Answer 1:

Bibliographic Information

Inhibitory effect of angiotensin II type 1 receptor antagonist on pancreatic cancer of nude mice. Jiang, Hua; Li, Zhao-shen; Xu, Guo-ming. Department of Gastroenterology, Changhai Hospital, Second Military Medical University, Shanghai, Peop. Rep. China. Dier Junyi Daxue Xuebao (2007), 28(6), 607-611. Publisher: Dier Junyi Daxue Xuebao Bianjibu, CODEN: DJXUE5 ISSN: 0258-879X. Journal written in Chinese. CAN 148:229667 AN 2007:1245294 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The objective of the paper is to investigate the inhibitory effect of selective angiotensin II type 1 receptor antagonist ZD7155 on pancreatic cancer xenografts of nude mice. Sixty nude mice were given s.c. injections of PaTu8988s cells to establish the pancreatic cancer xenograft models; then the animal models were evenly randomized into 3 groups: low-dose (10 mg/kg-1/d-1) ZD7155, high-dose (20 mg/kg-1/d-1) ZD7155 and normal saline groups. Ten mice in each group were sacrificed 10 d after treatment and the tumor sizes and body wts. were measured. The microvessel d. (MVD) was assessed by immunostaining of endothelial cells for CD31 and the cell apoptosis were obsd. by transmission electron microscope. Another thirty mice were treated for 30 days; the survival period of mice and toxicity of ZD 155 were obsd. till the 49th day of treatment. Results showed that ten days after treatment, the mean tumor vols. in the control, low-dose and high-dose groups were (35.8 ± 6.7) cm³, (21.5 ± 6.1) , cm³ and (10.7 ± 4.1) cm³, resp. ($P < 0.01$). The av. tumor inhibitory rates in low-dose and high-dose groups were 22.7% and 44.6%, resp., both significantly higher than that of the control group ($P < 0.01$). The mean nos. of capillary vessels in the control, low-dose and high-dose ZD7155 were 16.7 ± 0.9 , 11.5 ± 0.5 , and 6.05 ± 0.7 , resp. ($P < 0.01$). Transmission electron microscope showed a lot of typical apoptotic cells at different stages in the 2 ZD7155 treatment groups, whereas there was no apoptotic cells in the control group. The survival periods in treated groups were significantly longer than that in the control group ($P < 0.01$), and that of the high-dose group was longer than that of the low-dose group ($P < 0.01$). The toxicity of ZD7155 was not apparent. It was concluded that ZD7155 can inhibit the growth of pancreatic cancer in vivo through disturbing tumor angiogenesis and inducing tumor cell apoptosis. It may possibly serve as a safe and effective agent for treatment of pancreatic cancer.

Answer 2:

Bibliographic Information

Angiotensin-(1-7) Inhibits Growth of Human Lung Adenocarcinoma Xenografts in Nude Mice through a Reduction in Cyclooxygenase-2. Menon, Jyotsana; Soto-Pantoja, David R.; Callahan, Michael F.; Cline, J. Mark; Ferrario, Carlos M.; Tallant, E. Ann; Gallagher, Patricia E. Hypertension and Vascular Research Center and Departments of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC, USA. Cancer Research (2007), 67(6), 2809-2815. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 146:415568 AN 2007:289431 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Angiotensin-(1-7) [Ang-(1-7)] is an endogenous peptide of the renin-angiotensin system with vasodilator and antiproliferative properties. Our previous studies showed that Ang-(1-7) reduced serum-stimulated growth of human lung cancer cells in vitro through activation of a unique AT(1-7) receptor. The current study investigates the effect of Ang-(1-7) on lung tumor growth in vivo, using a human lung tumor xenograft model. Athymic mice with tumors resulting from injection of A549 human lung cancer cells were treated for 28 days with either i.v. saline or Ang-(1-7), delivered by implanted osmotic mini-pumps. Treatment with Ang-(1-7) reduced tumor vol. by 30% compared with the size before treatment; in contrast, tumor size in the saline-treated animals increased 2.5-fold. These results correlate with a redn. in the proliferation marker Ki67 in the Ang-(1-7)-infused tumors when compared with the saline-infused tumor tissues. Treatment with Ang-(1-7) significantly reduced cyclooxygenase-2 (COX-2) mRNA and protein in tumors of Ang-(1-7)-infused mice when compared with mice treated with saline as well as in the parent A549 human lung cancer cells in tissue culture. These results suggest that Ang-(1-7) may decrease COX-2 activity and proinflammatory prostaglandins to inhibit lung tumor growth. In contrast, the heptapeptide had no effect on COX-1 mRNA in xenograft tumors or A549 cells. Because Ang-(1-7), a peptide with

antithrombotic properties, reduces growth through activation of a selective AT(1-7) receptor, our results suggest that the heptapeptide represents a novel treatment for lung cancer by reducing COX-2.

Answer 3:

Bibliographic Information

Angiotensin II type 1 receptor antagonist candesartan as an angiogenic inhibitor in a xenograft model of bladder cancer.

Kosugi, Michio; Miyajima, Akira; Kikuchi, Eiji; Horiguchi, Yutaka; Murai, Masaru. Department of Urology, Keio University School of Medicine, Tokyo, Japan. *Clinical Cancer Research* (2006), 12(9), 2888-2893. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:369411 AN 2006:532570 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: There have been several studies on the antitumor activity of angiotensin II type 1 receptor (AT1R) antagonists. In this study, we evaluated the efficacy of the AT1R antagonist candesartan in bladder cancer. **Exptl. Design:** For the study in vitro, human bladder cancer cells (KU-19-19) were cultured with or without angiotensin II and candesartan. Various cytokines and cell viability were analyzed. For the study in vivo, a tumor xenograft model was prepd. in nude mice using KU-19-19 cells. Mice were given candesartan daily by oral gavage. Microvessel d., expression of vascular endothelial growth factor (VEGF), and apoptosis were assessed. **Results:** Candesartan did not induce direct toxicity in KU-19-19 cells, but VEGF and interleukin-8 were significantly lower in candesartan-treated cells (2.55 ± 0.25 and 6.58 ± 0.48 pg/103 cells) than in the angiotensin II - treated control cells (3.16 ± 0.42 and 7.91 ± 0.69 pg/103 cells). In mice, candesartan both at doses of 2 and 10 mg/kg/d significantly suppressed tumor growth in mice (35.4% and 33.5% redn. in tumor vol.). Microvessel d. was significantly decreased by candesartan (9.8 ± 2.8 per field) compared with the control group (17.6 ± 6.0 per field), and VEGF expression was significantly suppressed by this AT1R antagonist. However, candesartan did not induce apoptosis of cancer cells in the tumor. **Conclusions:** Specific blockade of AT1R prevented bladder tumor growth by inhibiting angiogenesis. However, its antitumor effect was not due to direct toxicity. Because AT1R antagonists are widely used to treat hypertension, and a 2 mg/kg/d dose level of candesartan is clin. achievable, this AT1R antagonist could also be used to treat bladder cancer.

Answer 4:

Bibliographic Information

Embryonic lethality in Dear gene-deficient mice: new player in angiogenesis. Herrera, Victoria L. M.; Ponce, Lorenz R. B.; Bagamasbad, Pia D.; VanPelt, Benjamin D.; Didishvili, Tamara; Ruiz-Opazo, Nelson. Section of Molecular Medicine, Department of Medicine and Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, MA, USA. *Physiological Genomics* (2005), 23(3), 257-268. Publisher: American Physiological Society, CODEN: PHGEFP ISSN: 1094-8341. <http://physiolgenomics.physiology.org/cgi/reprint/23/3/257.pdf> Journal; Online Computer File written in English. CAN 144:429577 AN 2006:213729 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The dual endothelin-1/angiotensin II receptor (Dear) binds endothelin-1 (ET-1) and angiotensin II (ANG II) with equal affinities in the Dahl S/JRHS rat strain. To elucidate its physiol. significance within the context of multiple receptor isoforms and diverse ET-1 and ANG II functions spanning blood pressure regulation, tumor proliferation, and angiogenesis, we characterized mouse Dear and Dear-deficient mice. Unlike nul mutant models of ET-1, ANG II, and all other ET-1 and ANG II receptors. Dear-/- deficiency results in impaired angiogenesis, dysregulated neuroepithelial development, and embryonic lethality by embryonic day 12.5. Interestingly, mouse Dear does not bind ANG II, similar to Dahl R/JRHS rat Dear, but binds ET-1 and vascular endothelial growth factor (VEGF) signal peptide (VEGFsp) with equal affinities, suggesting a putative novel multifunction for VEGFsp and a parsimonious mechanism for coordination of VEGF-induced and Dear-mediated pathways. Consistent with its developmental angiogenic role, Dear inhibition results in decreased tumor growth in B16-F10 melanoma cell-induced s.c. tumor in female Dear+/-/C57BL6BC10 mice, but not in males (age 3.5 mo), and in

¹²⁷Cs radiation-induced orthotopic mammary tumors in Sprague-Dawley female rats (age range 3-6.5 mo). Altogether, the data identify Dear as a new player in angiogenesis during development downstream to, and nonredundant with, VEGF-mediated pathways, as well as a putative modulator of tumor angiogenesis acting within a gender-specific paradigm.

Answer 5:

Bibliographic Information

Pharmacologic intervention with angiotensin II and kininase inhibitor enhanced efficacy of radioimmunotherapy in human colon cancer xenografts. Kinuya, Seigo; Yokoyama, Kunihiko; Kawashima, Atsuhiko; Hiramatsu, Takashi; Konishi, Shota; Shuke, Noriyuki; Watanabe, Naoto; Takayama, Teruhiko; Michigishi, Takatoshi; Tonami, Norihisa. Departments of Nuclear Medicine and Pathology, Kanazawa University School of Medicine, Kanazawa, Japan. *Journal of Nuclear Medicine* (2000), 41(7), 1244-1249. Publisher: Society of Nuclear Medicine, Inc., CODEN: JNMEAQ ISSN: 0161-5505. Journal written in English. CAN 134:68116 AN 2000:551017 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Induced hypertension and kininase inhibition can enhance tumor targeting of radiolabeled monoclonal antibody (MAb) by altering tumor circulation. This study investigated the effect of this manipulation on the antitumor efficacy of radioimmunotherapy (RIT). **Methods:** Mice bearing human colon cancer xenografts were administered 2.0 µg/kg/min of angiotensin II (AT-II) for 1 h and 30 µg of a kininase inhibitor, enalapril maleate, before the administration of 3.7 MBq ¹³¹I-A7, an IgG1 against 45-kDa glycoprotein on colorectal cancer, and tumor growth was obsd. thereafter. The mechanism of the manipulation effect was investigated by estn. of the tissue absorbed dose and radioluminog. of tumors. **Results:** The pharmacol. manipulation with AT-II and enalapril improved the tumor quadrupling time (T_q) of 3.7 MBq RIT from 24.3 ± 2.75 d to 33.1 ± 2.83 d (P < 0.05). Addn. of this manipulation made 3.7 MBq RIT as effective as 9.25 MBq RIT alone (T_q, 37.2 ± 2.97 d). Dose estn. showed that the manipulation increased the tumor absorbed dose 1.55-fold without affecting the doses to normal tissues. Uniform intratumoral distribution in the manipulated tumors was shown by radioluminog. **Conclusion:** Larger and more uniform tumor radiation produced by this pharmacol. manipulation can benefit RIT with ¹³¹I-MAb.

Answer 6:

Bibliographic Information

Effect of angiotensin II on immunotoxin uptake in tumor and normal tissue. Elizondo, Felipe G., Jr.; Sung, Cynthia. National Center Research Resources, National Institutes Health, Bethesda, MD, USA. *Cancer Chemotherapy and Pharmacology* (1996), 39(1/2), 113-121. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 126:326034 AN 1997:262006 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effect of the sarcosine analog of human angiotensin II ({sar}ATII) on the uptake and spatial distribution of immunotoxins (mol. wt. 210,000 Da) in RD rhabdomyosarcoma xenografts in mice was investigated. A period of elevated blood pressure of approx. 80 min, measured by noninvasive photoplethysmog., was achieved by a 40-min continuous i.p. infusion of {sar}ATII at 0.07 µg/min. Tumor-bearing animals were injected i.v. with ¹²⁵I-labeled specific and ¹³¹I-labeled nonspecific immunotoxins and made hypertensive by i.p. infusion of {sar}ATII. Radioactivity was measured in blood plasma, tumor, liver, kidney, and muscle at 2, 6, and 24 h. Blood plasma radioactivity was subtracted from tissue values to calc. tissue uptake. To assess the spatial distribution of immunotoxin in the solid tumor, ¹²⁵I-labeled specific immunotoxin was injected i.v. into tumor-bearing animals, and quant. autoradiog. was performed on tumor sections. Uptake of specific or nonspecific immunotoxins in tumor and normal tissues was not different in {sar}ATII-hypertensive animals compared with saline-treated controls. Spatial distribution of ¹²⁵I-labeled specific immunotoxins was very heterogeneous in control animals and contained punctate accumulations throughout the tumor. Treatment with {sar}ATII did not affect this distributions qual. or quant. Interstitial pressure in the RD tumor was only 0.6 mm Hg, measured using a fluid-filled micropipette connected to a servo-null pressure transducer. The sustained period of {sar}ATII-induced hypertension had no effect on RD tumor or normal tissue uptake, or tumor spatial distribution of immunotoxin. Heterogeneity of immunotoxin distribution in saline-treated controls did not arise from an elevated interstitial pressure

Answer 7:

Bibliographic Information

Effect of induced hypertension with angiotensin II infusion on biodistribution of ¹¹¹In-labeled monoclonal antibody.

Kinuya, Seigo; Yokoyama, Kunihiko; Konishi, Shota; Tonami, Norihisa; Hisada, Kinichi. SCHOOL MEDICINE, KANAZAWA UNIVERSITY, Kanazawa, Japan. Nuclear Medicine and Biology (1996), 23(2), 137-40. Publisher: Elsevier, CODEN: NMBIEO ISSN: 0883-2897. Journal written in English. CAN 124:311291 AN 1996:224929 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We investigated whether induced hypertension could enhance tumor uptake of monoclonal antibody. ¹¹¹In-DTPA-A7 (IgG1 against 40 kD tumor assocd. glycoprotein) was injected into colon carcinoma xenografted mice which were s.c. implanted with micro-osmotic pump contg. angiotensin II (AT-II). Biodistribution was obsd. in groups of mice infused with AT-II at rate of 0.5 µg/kg/min (L) or 1 µg/kg/min (H) and compared with a group of mice infused with saline (S). Tumor uptake of ¹¹¹In-A7 in L and H was 1.32 and 1.57 times greater than S at 48 h after i.v. injection of A7. Normal organ uptakes also tended to be increased by AT-II infusion. Further study is needed to get optimum effect of hypertensive treatment on biodistribution of radiolabeled MoAb.

Answer 8:

Bibliographic Information

Pharmacologic modification of tumor blood flow and interstitial fluid pressure in a human tumor xenograft: network analysis and mechanistic interpretation.

Zlotecki, Robert A.; Baxter, Laurence T.; Boucher, Yves; Jain, Rakesh K. Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA. Microvascular Research (1995), 50(3), 429-43. Publisher: Academic, CODEN: MIVRA6 ISSN: 0026-2862. Journal written in English. CAN 124:164696 AN 1996:20797 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Various vasoactive agents have been used to modify tumor blood flow with the ultimate goal of improving cancer detection and treatment, with widely disparate results. Furthermore, the lack of mechanistic interpretations has hindered understanding of how these agents affect the different physiol. parameters involved in perfusion. Thus, there is a need to develop a unified framework for understanding the interrelated physiol. effects of pharmacol. and phys. agents. The goals of this study were (1) to develop a math. model which helps det. the location and magnitude of changes in the vascular resistance of tumor and normal tissues and (2) to test the model with the authors own exptl. studies and by comparison with results from the literature. The systemic and interstitial pressures and relative tumor blood flow were measured before and after administration of angiotensin II, epinephrine, norepinephrine, nitroglycerin, and hydralazine in SCID mice bearing LS174T human colon adenocarcinoma xenografts. A math. model was developed in analogy to elec. circuits which examd. the pressure, flow, and resistance relationships for arterial and venous segments of the vasculature of a tumor and surrounding normal tissue. Vasoconstrictor-induced increases in the mean arterial blood pressure led to increases in tumor blood flow and interstitial pressure with the magnitude of change dependent on the agent (percentage change in blood flow: angiotensin > epinephrine > norepinephrine). The vasodilating agents induced decreases in tumor blood flow in parallel to the induced decreases in the systemic pressure, but only the long-acting arterial vasodilator hydralazine was capable of effecting a decrease in tumor interstitial pressure. The model was also consistent with other data available in the literature on norepinephrine, pentoxifylline, nicotinamide, and hemodilution, and was useful in providing input as to the location and degree of the physiol. effects of these agents.

The results of the data and model show that the steal phenomenon is the dominant mechanism for redistribution of host blood flow to the tumor. However, some degree of arterial control was present in the tumors. Moreover, the parallel increases in tumor interstitial pressure and blood flow contradict any hypothesis suggesting that elevated interstitial fluid pressure ppts. chronic vascular collapse, thus decreasing blood flow.