Kumamoto University Medicine/Bioscience Seminar

医学・生命科学セミナー

日程：平成２１年９月１日（火）　１７：３０～

場所：医学教育図書棟３階　第１講義室

注）場所が変更になってます!!

「ヒトにおける発がん、特に放射線誘発肝腫瘍の分子機構」

講師：福本　学　先生（東北大学加齢医学研究所　病態臓器構築研究分野　教授）

＊＊＊＊抄録＊＊＊＊

Irradiation from internally deposited radionuclides induces malignant tumors. Ingested radionuclides accumulate in specific organs which are irradiated over a lifelong period. Thorotrast is a 25% colloidal solution of natural α-emitter, thorium dioxide used as a radiological contrast medium during World War II. It caused hepatic malignant tumors by the local exposure to α-particles from deposited Thorotasrt in the liver decades after administration. Thorotrast-induced liver tumors consist of intrahepatic cholangiocarcinoma (ICC), angiosarcoma (AS) and hepatocellular carcinoma (HCC), at nearly the same instance. More than 80% of malignant liver tumors unrelated to radiation in Japan consist of HCC, indicating that ICC and AS are index tumors of radiation-induced liver tumors. We analyzed mutations of the *p53* and the K-*ras* genes, microsatellite instability (MSI), and loss of heterozygosity (LOH) in Thorotrast ICC (Th-ICC). The major *p53* mutation observed in Th-ICC was the transition type, suggesting that reactive oxygen species are not likely involved in gene mutations of Thorotrast induced cancers. MSI frequency in Th-ICC was significantly higher than that in non-Th-ICC. MSI was partly attributed to the inactivation of the *hMLH1* mismatch repair gene via methylation of its promoter region and to monoclonal expansion of cells with mutations. Th-ICC shared LOH pattern with non-Th cholangiolocelluar carcinoma, suggesting that Th-ICC originates from an *in situ* stem cell which can differentiate into hepatocytes and epithelial cells of intrahepatic ducts. The distribution of thorium deposits was not always consistent with that of apoptotic cells. Autoradiography of liver tissues with Th-ICC showed that the density of α-tracks was far more concentrated than would be expected if Thorotrast were evenly distributed throughout the liver. We think that three major factors are responsible for the long incubation time: uneven distribution of radionuclides, limited range of irradiation and dynamic movement of tumor precursor cells. We hypothesize that target cells susceptible to malignant transformation may undergo one event by exposure to α-particles and may then migrate outside of the range of α-particles, thereby avoiding immediate induction of successive additional events that would lead to cell death or neoplastic changes. We conclude that Th-ICC is developed through complex carcinogenic steps including genomic instability and mutations of crucial genes during remodeling of the liver architecture. We emphasize how pathological specimens from Thorotrast patients are valuable for assessing radiation carcinogenesis by internally deposited radionuclides.

I would also touch on our recent work on the establishment of clinically relevant radioresistant cells for the development of better radiotherapy.

世話分野：細胞病理学分野
教　　授：竹屋　元裕　先生
E - Mail：takeya@kumamoto-u.ac.jp

Kumamoto University

Academic Year 2009

Medicine/Bioscience Seminar

Date : September 1, 2009 (tue) 17:30～

Place : Lecture Room 1
(Medical Education & Library Building 3F)

Please note that the place has been changed.

「Molecular genetic mechanisms of human cancer focused on radiation-induced liver tumors」

Prof. Manabu Fukumoto (Tohoku University, IDAC, Dept. Pathology)

★★★★★ Abstract ★★★★★

Irradiation from internally deposited radionuclides induces malignant tumors. Ingested radionuclides accumulate in specific organs which are irradiated over a lifelong period. Thorotrast is a 25% colloidal solution of natural α-emitter, thorium dioxide used as a radiological contrast medium during World War II. It caused hepatic malignant tumors by the local exposure to α-particles from deposited Thorotasrt in the liver decades after administration. Thorotrast-induced liver tumors consist of intrahepatic cholangiocarcinoma (ICC), angiosarcoma (AS) and hepatocellular carcinoma (HCC), at nearly the same instance. More than 80% of malignant liver tumors unrelated to radiation in Japan consist of HCC, indicating that ICC and AS are index tumors of radiation-induced liver tumors. We analyzed mutations of the *p53* and the K-*ras* genes, microsatellite instability (MSI), and loss of heterozygosity (LOH) in Thorotrast ICC (Th-ICC). The major *p53* mutation observed in Th-ICC was the transition type, suggesting that reactive oxygen species are not likely involved in gene mutations of Thorotrast induced cancers. MSI frequency in Th-ICC was significantly higher than that in non-Th-ICC. MSI was partly attributed to the inactivation of the *hMLH1* mismatch repair gene via methylation of its promoter region and to monoclonal expansion of cells with mutations. Th-ICC shared LOH pattern with non-Th cholangiolocelluar carcinoma, suggesting that Th-ICC originates from an *in situ* stem cell which can differentiate into hepatocytes and epithelial cells of intrahepatic ducts. The distribution of thorium deposits was not always consistent with that of apoptotic cells. Autoradiography of liver tissues with Th-ICC showed that the density of α-tracks was far more concentrated than would be expected if Thorotrast were evenly distributed throughout the liver. We think that three major factors are responsible for the long incubation time: uneven distribution of radionuclides, limited range of irradiation and dynamic movement of tumor precursor cells. We hypothesize that target cells susceptible to malignant transformation may undergo one event by exposure to α-particles and may then migrate outside of the range of α-particles, thereby avoiding immediate induction of successive additional events that would lead to cell death or neoplastic changes. We conclude that Th-ICC is developed through complex carcinogenic steps including genomic instability and mutations of crucial genes during remodeling of the liver architecture. We emphasize how pathological specimens from Thorotrast patients are valuable for assessing radiation carcinogenesis by internally deposited radionuclides.

I would also touch on our recent work on the establishment of clinically relevant radioresistant cells for the development of better radiotherapy.

Invitor : Cell Pathology
Professor : Prof. Motohiro Takeya
E-Mail : takeya@kumamoto-u.ac.jp